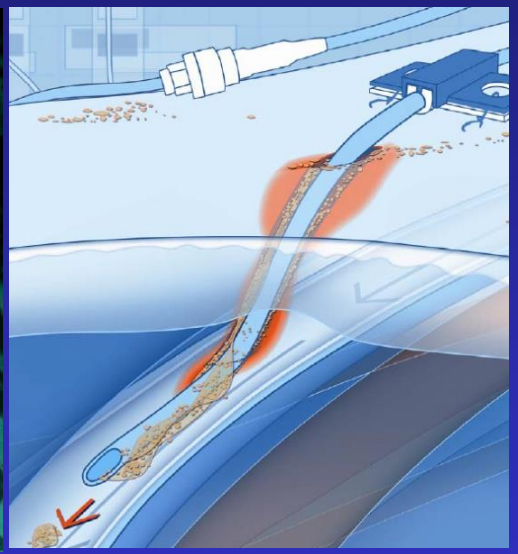
Übersicht zur Problematik Katheter-assoziierter Infektionen – unter besonderer Berücksichtigung Rifampicin-Miconazol-inkorporierter Katheter



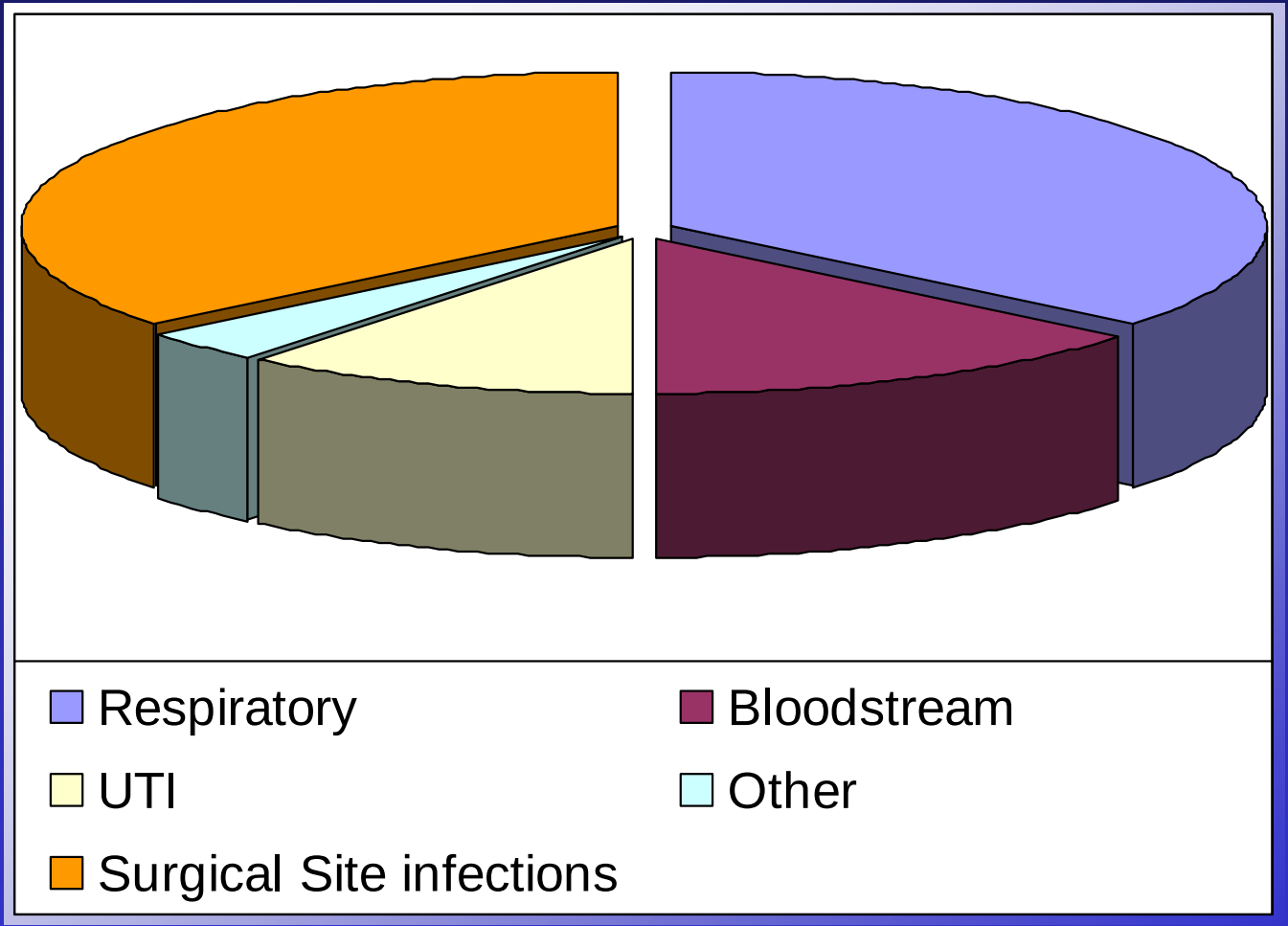
Priv.-Doz. Dr. med. Dr. rer.nat. Jörg M. Schierholz
BVMed Berlin Krankenhaushygiene

Presentation 2013

Übersicht

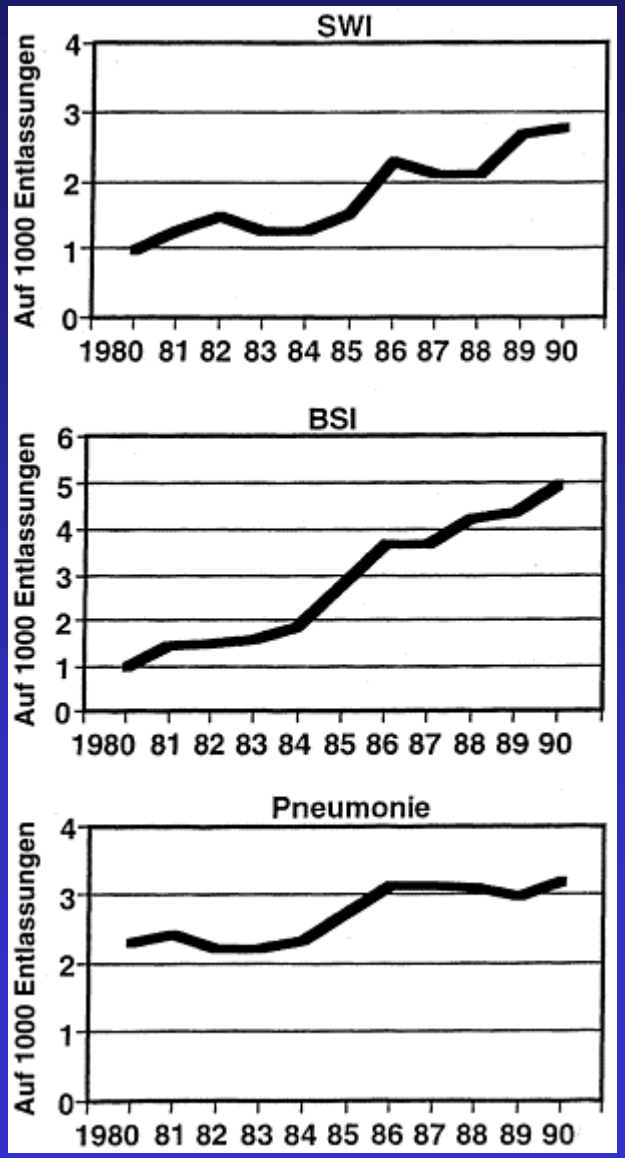
- Ätiologie, Pathogenese und klinische Relevanz von Fremdkörperinfektionen
- Innovative, antimikrobielle Materialien – eine Übersicht
- Präklinische und klinische Wirksamkeit innovativer Katheterbeschichtungen, Meta-analysen; Wirtschaftlichkeitsanalysen

Total Nosocomial Infections - $24-44 Billion annually



Infection Control and Biosafety. Trends, Products and Opportunities. Medical Data International 2003
Scott et al. Columbia University 2010

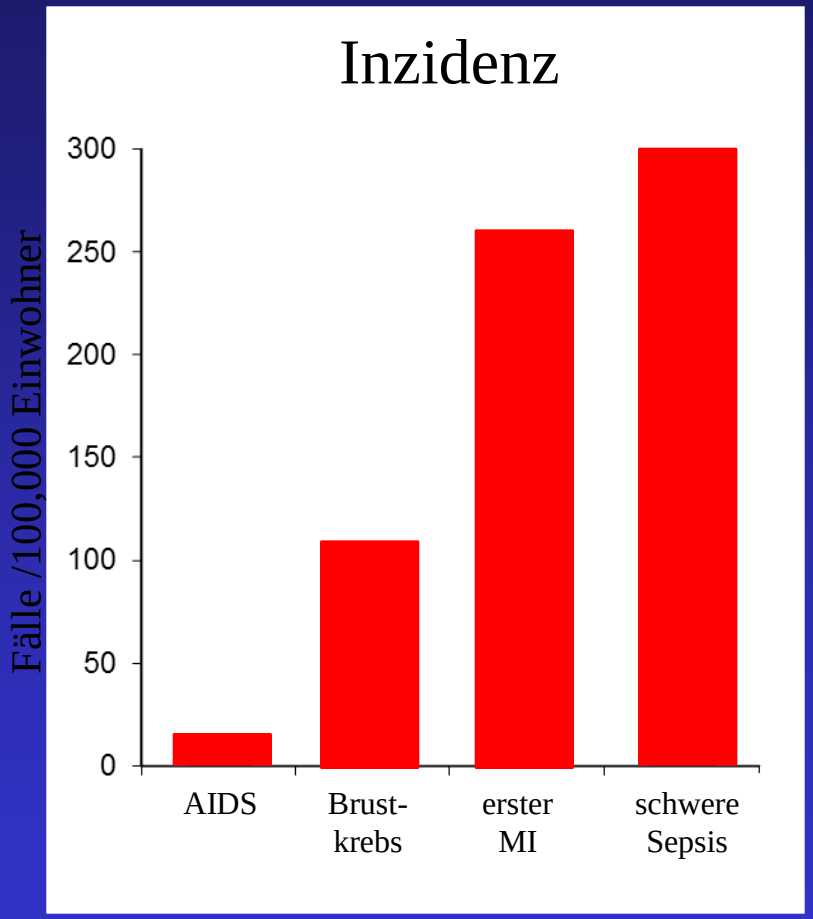
Infections-Numbers

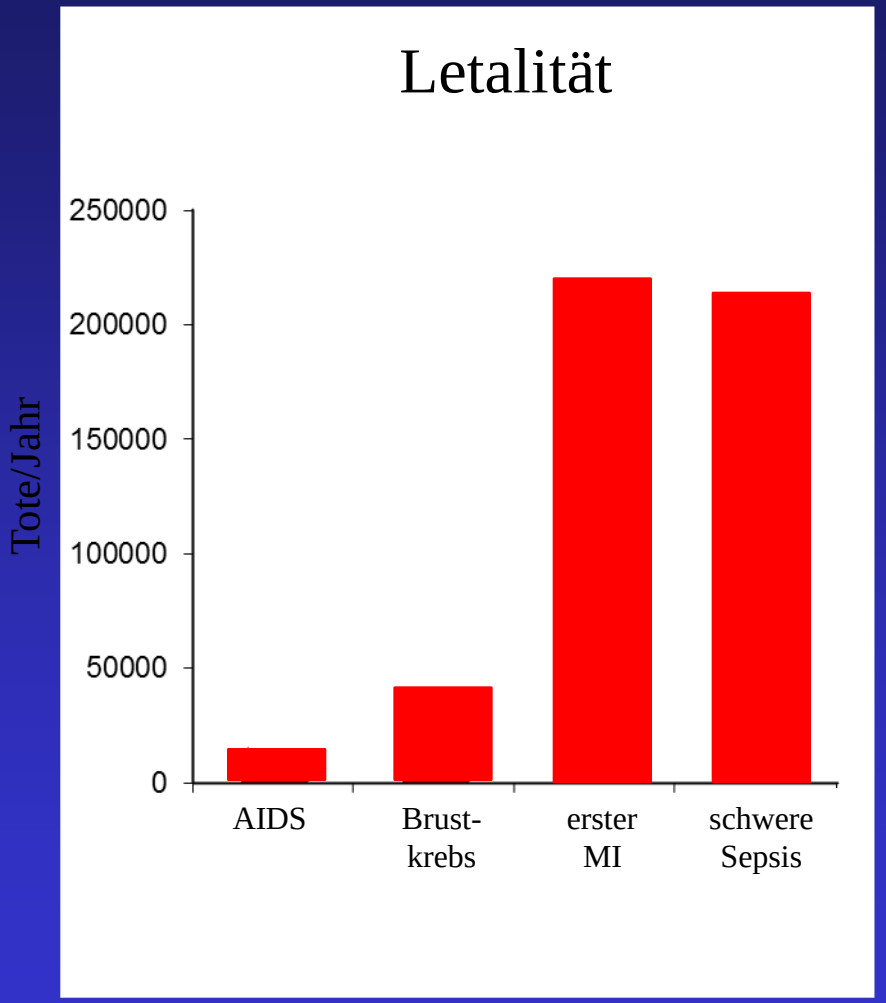


Infections	(%)
Hospital Patients	5-15%
ICU patients	25-40%
Mortality increase 10 years	58%
Nosoc. Inf./a Ger	600000
Sepsis cases	20-90.000

Moerer et al. Intensive Care Med. 2002 Oct;28(10):1440-6.

Schwere Sepsis: Inzidenz und Letalität



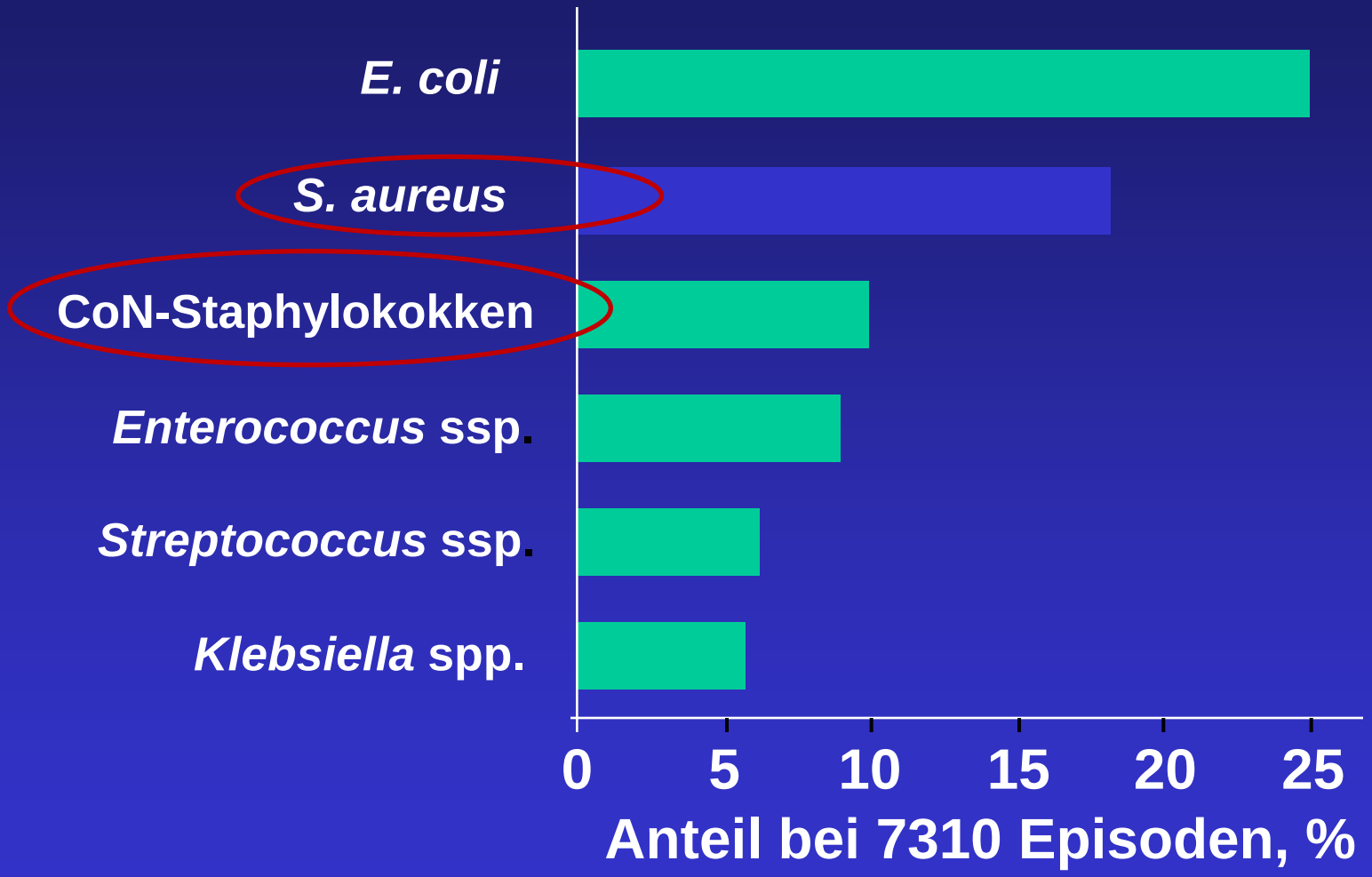


Angus DC, Linde-Zwirble WT, Lidicker J, et al. Incidence, cost and outcomes of severe sepsis in the United States. Crit Care Med 2001

American Heart Association. 2001 Heart and Stroke Statistical Update. Dallas, Tex:

American Cancer Society. Cancer Statistics. Online edition, accessed 3/29/01.

PEG-Blutkulturstudie



Becker et al., Chemother J 19: 28-39, 2010

CRBSI

Healthcare (ICU)-associated BSI

Study (no. of BSI)	Primary (NK)	Secondary	CRBSI
1 (104)	21	60	19
2 (111)	27	38	35
3 (329)	22	16	62
4 (111)	29	45	26
5 (105)†	61	18	21
Total 760	**30% (22-61)**	**29% (16-60)**	**41% (19-62)**

† ICU and surgical wards

1. Pittet et al JAMA 1994 **271**:1598
2. Rello et al Intensive Care Med 1994 **29**:94
3. Edgeworth et al Crit Care Med 1999 **27**:1421
4. Renaud et al Am J Respir Crit Care Med 2001 **163**:1584
5. Orsi et al Infect Control Hosp Epidemiol 2002 **23**:190

Catheter-related infections- magnitude of the problem

- CRBSI: 1.4 – 25/1.000 catheter days (1)
- Mortality rate: 0.3 -24%.(1)
- Costs: 11,900$- 56.000$/ CRBSI (2)

- Prevention of one CRBSI: 2,4 ICU days and 7,5 hospital days reduction
- CRBSI 75% reduction: Cost savings of 227$/antimicrobial CVC (3)

1 D.Maki et al., The risk of bloodstream infection in adults with different intravascular devices: A systematic review of 200 published prospective studies, Mayo Clin Proc. 81(9): 1159-1171, 2006 2 Blot SI, Depuydt P. Annemans L, et al. Clinical and economic outcomes in critically ill patients with nosocomial catheter-related bloodstream infections. Clin Infect Dis1;41:1591-1598, 2005 3 Hockenhull JC, Dwan K, Boland A, Smith G, Bagust A, Dündar Y, Gamble C, McLeod C, Walley T, Dickson RThe clinical effectiveness and cost-effectiveness of central venous catheters treated with anti-infective agents in preventing bloodstream infections: a systematic review and economic evaluation. Health Technol Assess.;12(12):iii-iv, xi-xii, 1-154, 2008.

Patient groups with higher CRBSI rates

•Oncology/Transplantation:	2 – 8 CRBSI/1.000 catheter days
•Paediatric oncology:	4 – 20 CRBSI/1.000 catheter days
Neonatology:	4.4 – 17 CRBSI/1.000 catheter days
•Paediatrics:	4.4 - 12.8 – 25/1.000
>2500g <1.000g	
•Dialysis:	4.8 – 8.5 BSI/1.000 catheter days
• Parenteral nutrition:	5 – 8 CRBSI/1.000 catheter days
• Burns Unit:	15 – 30/1,000 catheter days

D.Maki et al., The risk of bloodstream infection in adults with different intravascular devices: A systematic review of 200 published prospective studies, Mayo Clin Proc. 81(9): 1159-1171, 2006 R.Vilela et al. Risk factors for central venous catheter–related infections in pediatric intensive care. Clinics, 62(5): 537-44, 2007 Crnich, Christopher J; Kluger, Daniel M; Maki, Dennis G The Risk of Bloodstream Infection in Adults With Different Intravascular Devices: A Systematic Review of 200 Published Prospective Studies Mayo Clin Proc.;81(9):1159-1171, 2006

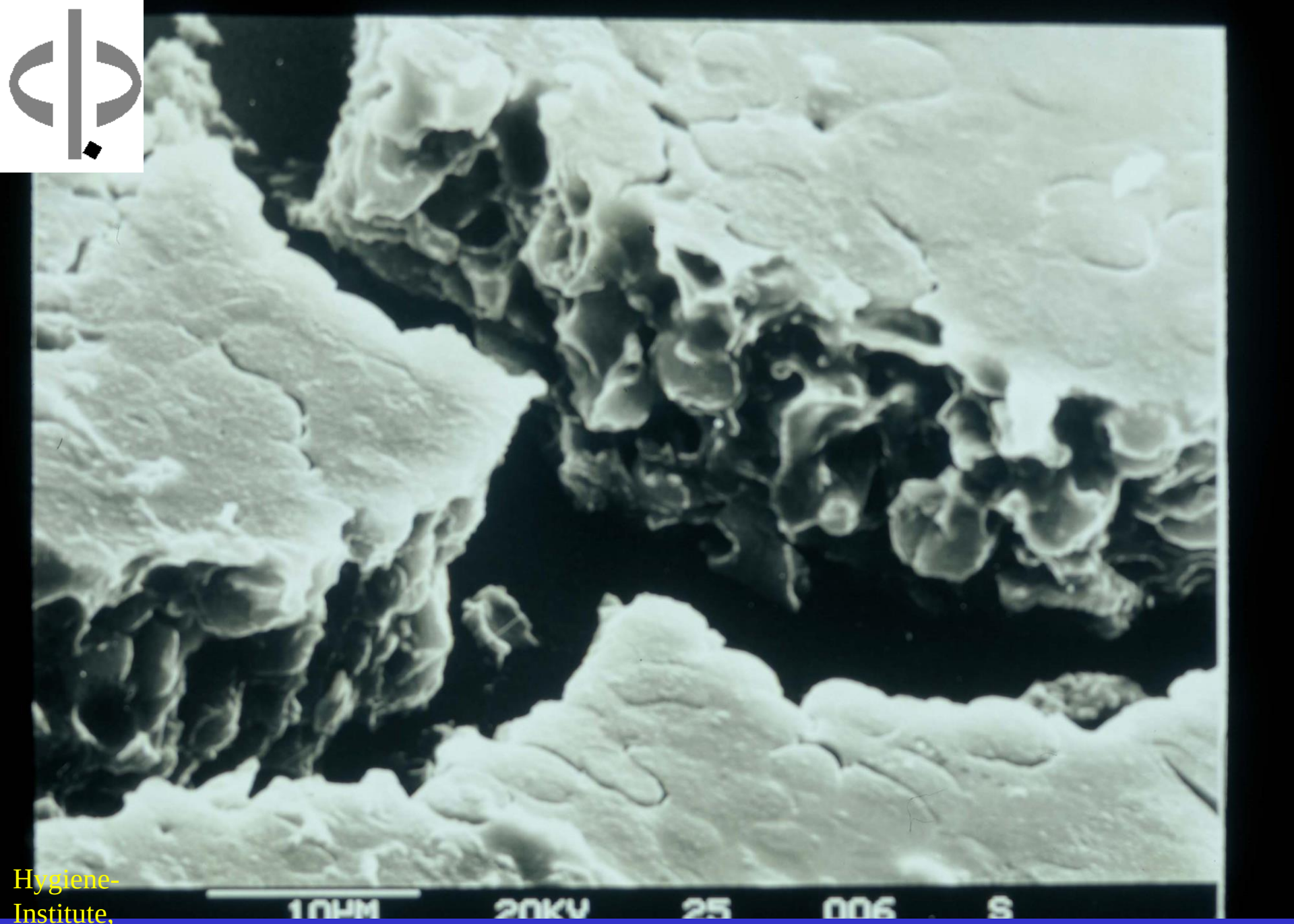
Infection-Economy in German University ICUs

Total Costs

• ICU bed /day	1,600-3500
• Medical devices/disposables	40$
• Personal costs/patient	1000-4000$
• 20% heavy cases	80% of costs
Sepsis patients	14-40% costs
• 8% mortality	23% of costs

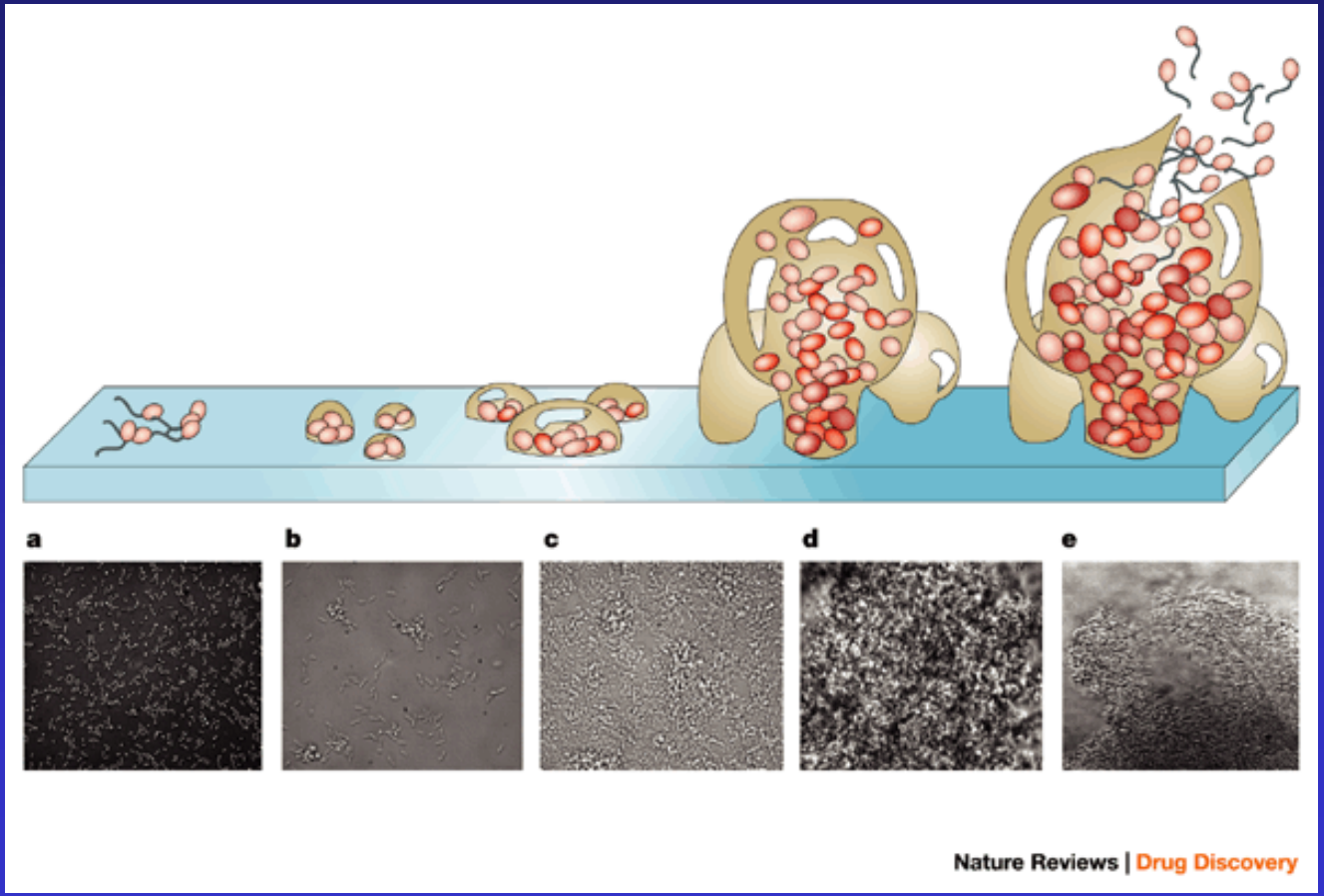
Moerer et al. Intensive Care Med. 2002 Oct;28(10):1440-6.


Hygiene-Institute,
cologne



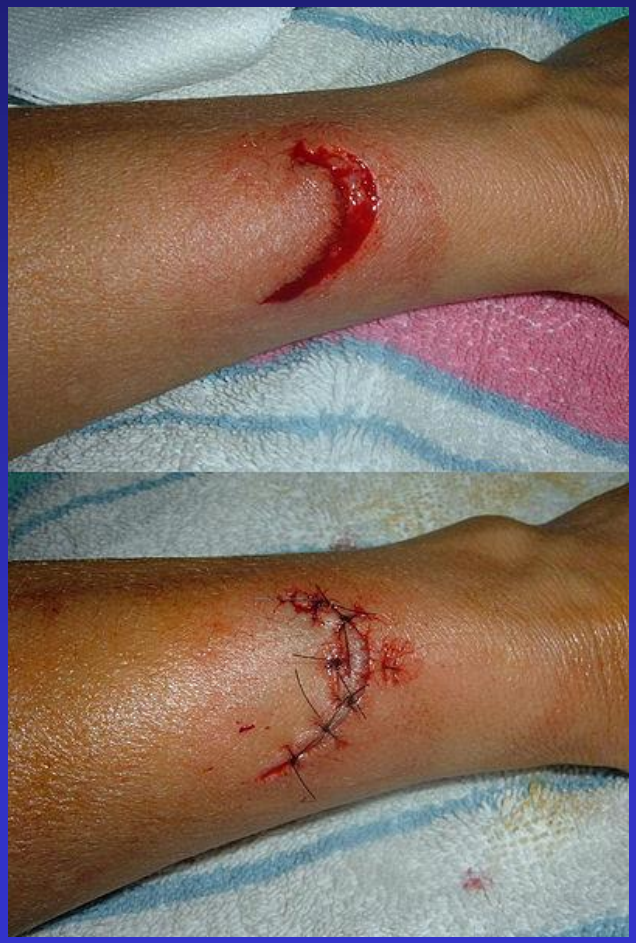
Hygiene-Institute, Cologne

Biofilm characteristics



http://www.nature.com/nrd/journal/v2/n2/images/nrd1008-f1.gif

Pioneers in foreign-body infections:

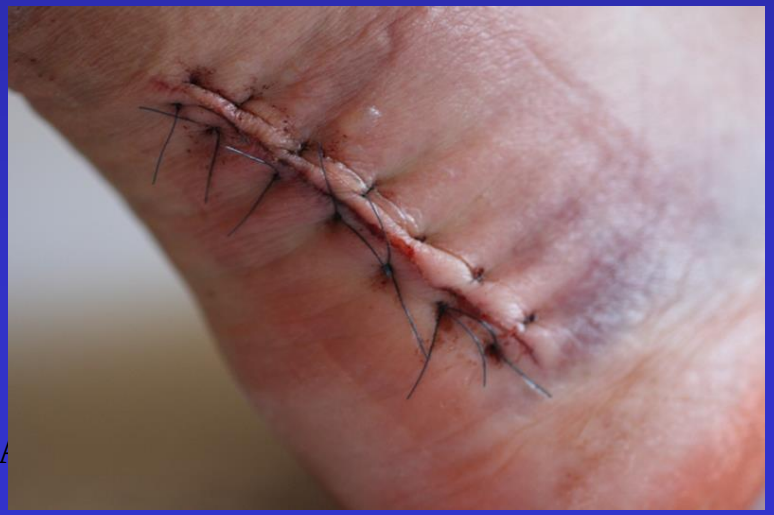


THE VIRULENCE OF *STAPHYLOCOCCUS PYOGENES* FOR MAN.
A STUDY OF THE PROBLEMS OF WOUND INFECTION

S. D. ELEK AND P. E. CONEN
From the Department of Bacteriology, St. George's Hospital Medical School (University of London), London, S.W.1

Received for publication 9 August, 1957

LITTLE direct evidence is available about the virulence of strains of *Staph. pyogenes* to man. Garrè (1885) infected himself with a strain obtained from a fatal case of osteomyelitis by rubbing a whole slope culture into the skin of the left forearm. Small pustules appeared around the hair follicles within a few hours, which enlarged and eventually coalesced into a large carbuncle, which took three weeks to heal with much scar formation. Similar experiments were carried out subsequently by Rümm (1885) and by Rockhart (1887). In this



Immunology of Implant Healing and Implants Infection

- phase variation – higher virulence
- dormancy – high antibiotic resistance

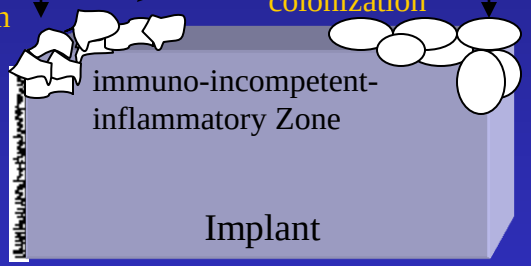
Bacteria:

- extracapsulare exopolysaccharides
  → physico–chemical binding of antibiotics

Fibroblasts

Factors delay wound healing

- neutrophil inhibitor factor
- decreased antibody response by poor immunogenicity of S.epidermidis



Neutrophils, macrophages:

- low IFγ - IL_2 – release
- suppressed MHC II – expression
- triggering a preempt of super-oxide production by the presence of implant materials

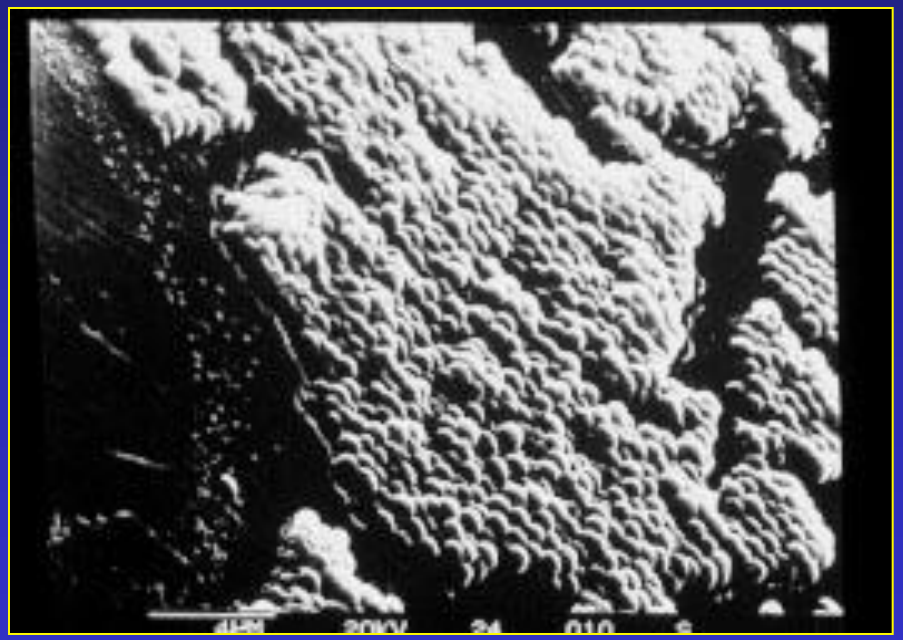
Adsorbed macromolecules:

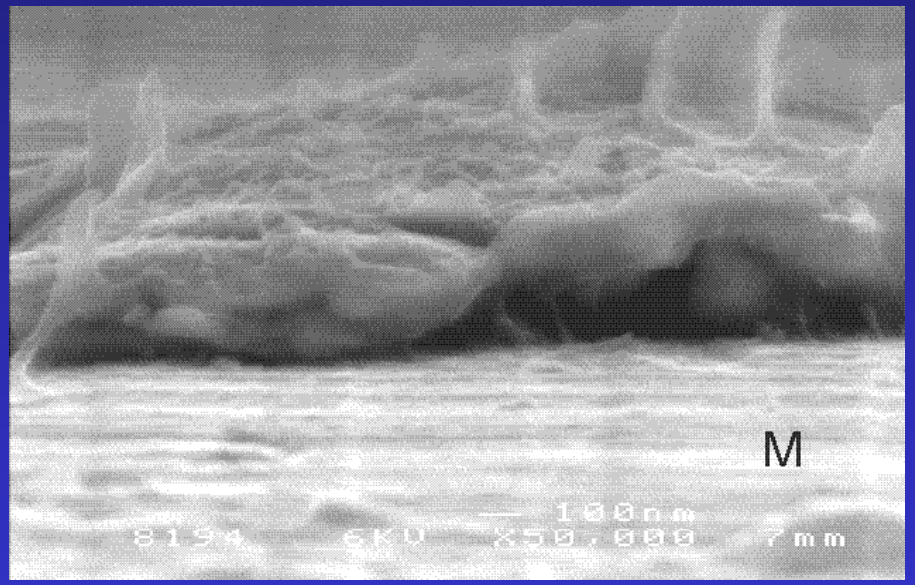
(relationship albumin, globulin, fibronectin, fibrinogen):

inflammatory-
antiinflammatory properties

Schierholz et al., J.Hosp.Inf. 2001

Race for the surface
Bacterial colonization vs healing



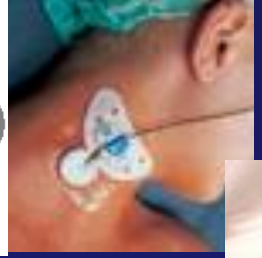


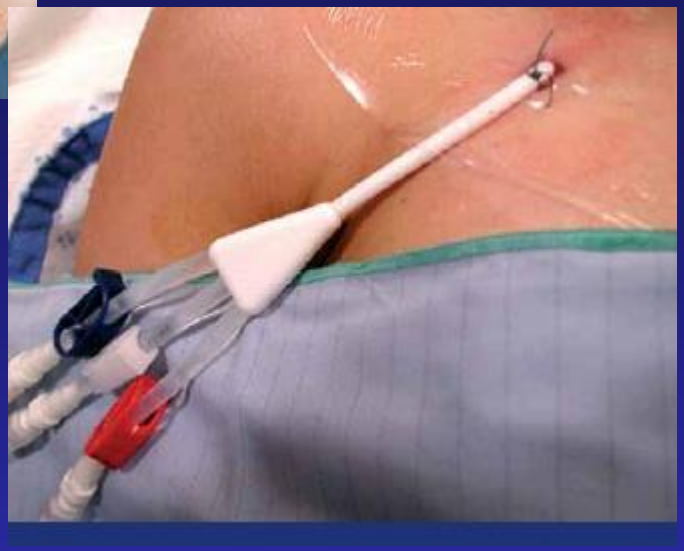
Schierholz et al.
Deutsches Ärzteblatt
1998

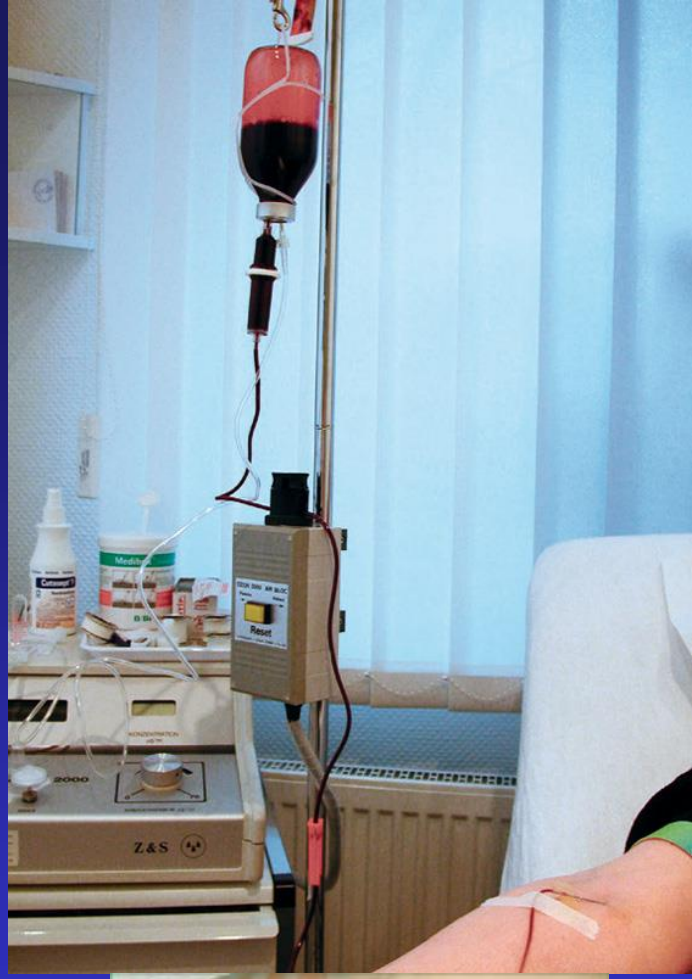
Critical Implants

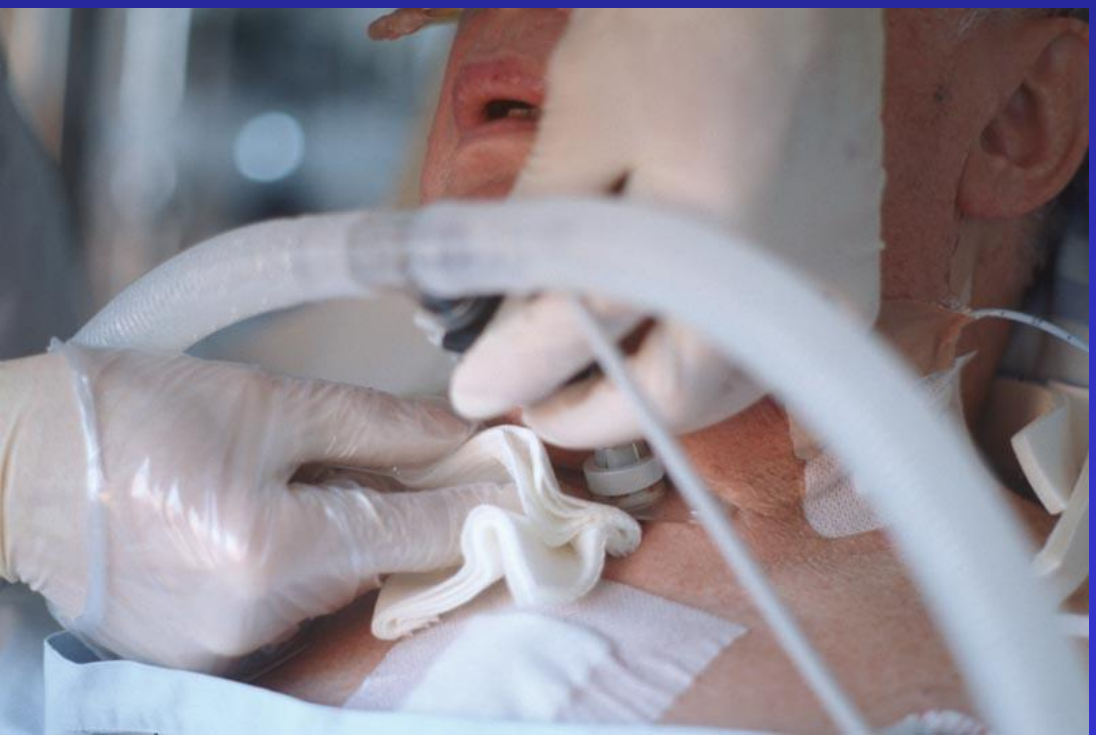
Incidence of Implant - associated Infections

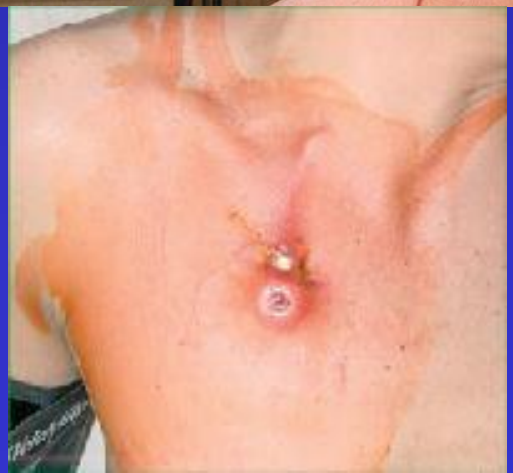
Implant		Applications/Year	Infection Rate[%]	(median)[%]
Hip prostheses		1.000.000	0.5-3	(1.5)
Arterial Grafts		800.000	0.2-13.9	(1.5)
Cardiac valves	>	300.000	0.2-2	(1.8)
Pacemaker-electrodes	>	1.000.000	0.5-4	(3)
Artificial heart	>	10.000	10-100	(20)
Fixateure externe (Pin)			5-15	(10)
CSF shunts		50.000	5-10	(8)



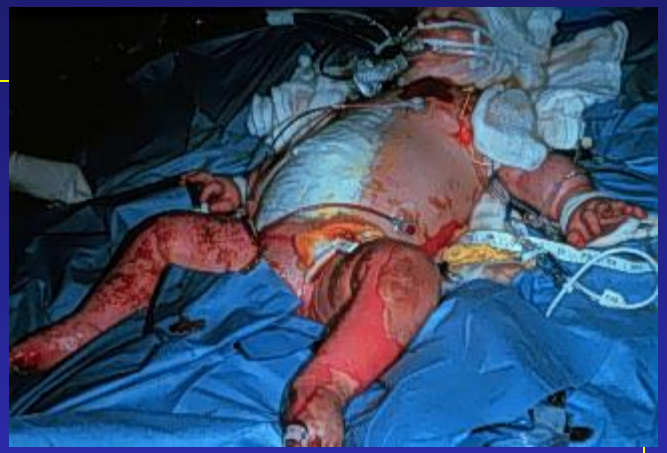


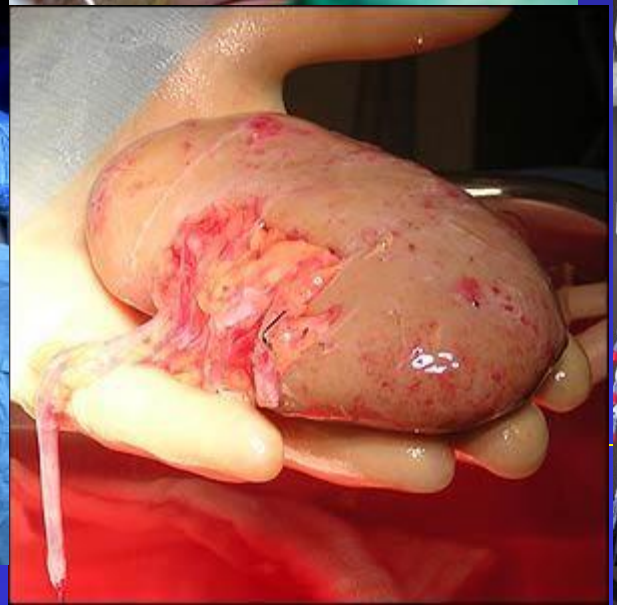

Reset
Z&S



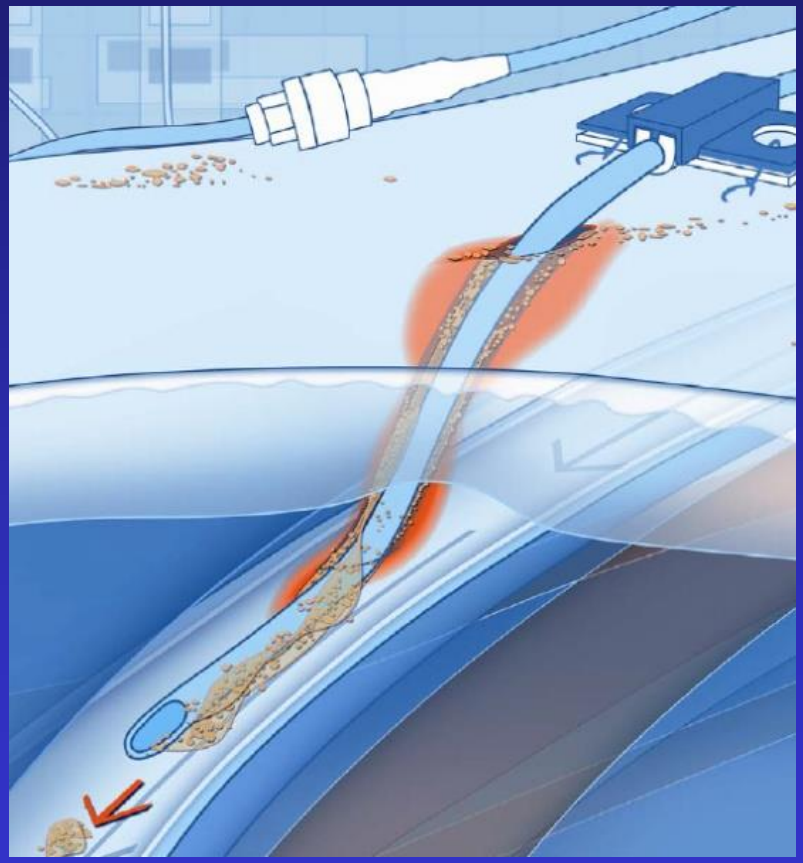


Critically ill patients groups with high CRBSI





Pathogenesis: Routes of CRI



CRBSI-Risk factors

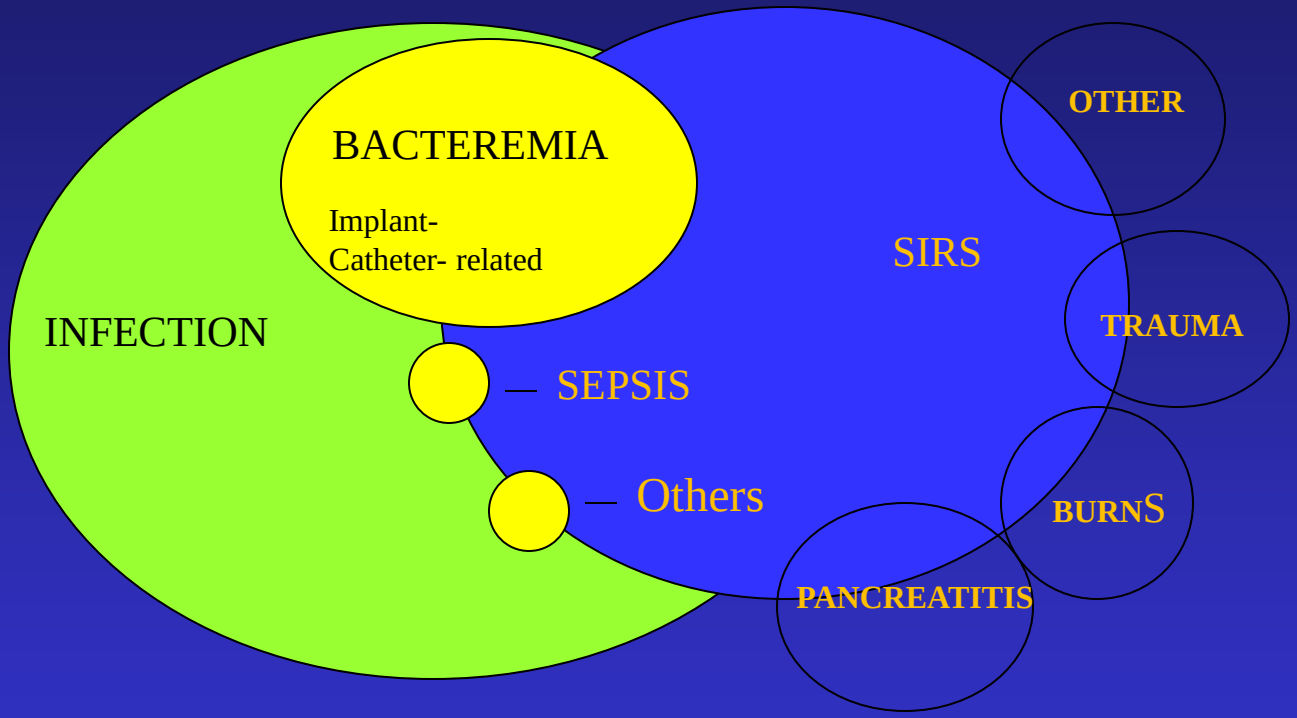
1. Prolonged hospitalization before central vein catheter insertion.
2. Prolonged duration of catheterization.
3. Heavy growth of bacteria at the insertion site and the catheter hub.
4. Catheters inserted in the femoral vein and internal jugular vein.

Causes of catheter-associated bloodstream infection

1. Contaminated hands of health-care personnel.
2. Catheter contamination on insertion.
3. Hub colonization.
4. Spread of bacteria through the bloodstream.
5. Patient's skin flora.
6. Contaminated IV fluids.

Warren DK et al. Chest 2004 Nov;126(5):1612-8

Definition For Sepsis and Organ Failure



Interrelationships among Systemic Inflammatory Response Syndrome (SIRS), Sepsis and Infection in ICUs.

CDC Diagnostics

- catheter colonization: pos. quantit. culture (catheter, hub, lumen) and no local infection signs
- local catheter infection: prurulence, cellulitis, pos. SQM + phlebitis or fever (≥ 38° C), pos. blood culture through catheter + phlebitis or fever (≥ 38° C)
- CRI: C-exite site infection + peripheral blood culture, same bacteria
- pericatheter cellulitis + primary bacteriemia (CDC)
- positive blood culture catheter + peripheral positive culture, same organism
- paired quantitative blood cultures through catheter 5 fold the peripheral number

*www.**cdc**.gov/hicpac/bsi/bsi-guidelines-2011.html*

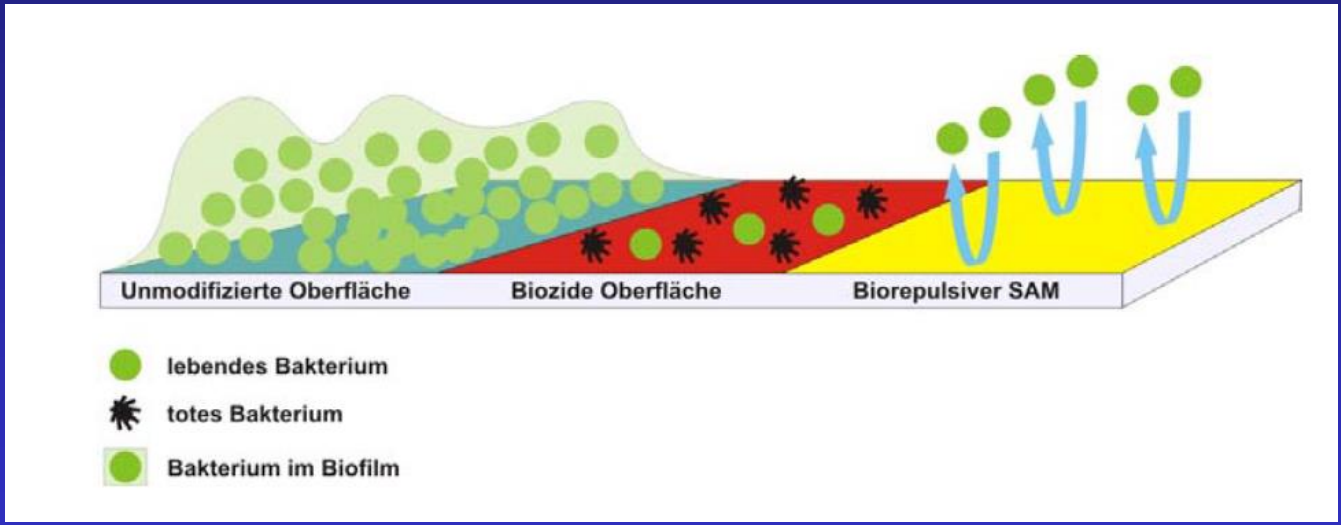
Infection control strategies- hygienic measures

BSI Prevention Bundle

Avoid unneccessary lines
Hand hygiene
Maximal sterile barrier
CHX skin prep.
Avoid fem. Lines — CDC MMWR 2002
CHG dressing? — Timsit et al. JAMA 2009

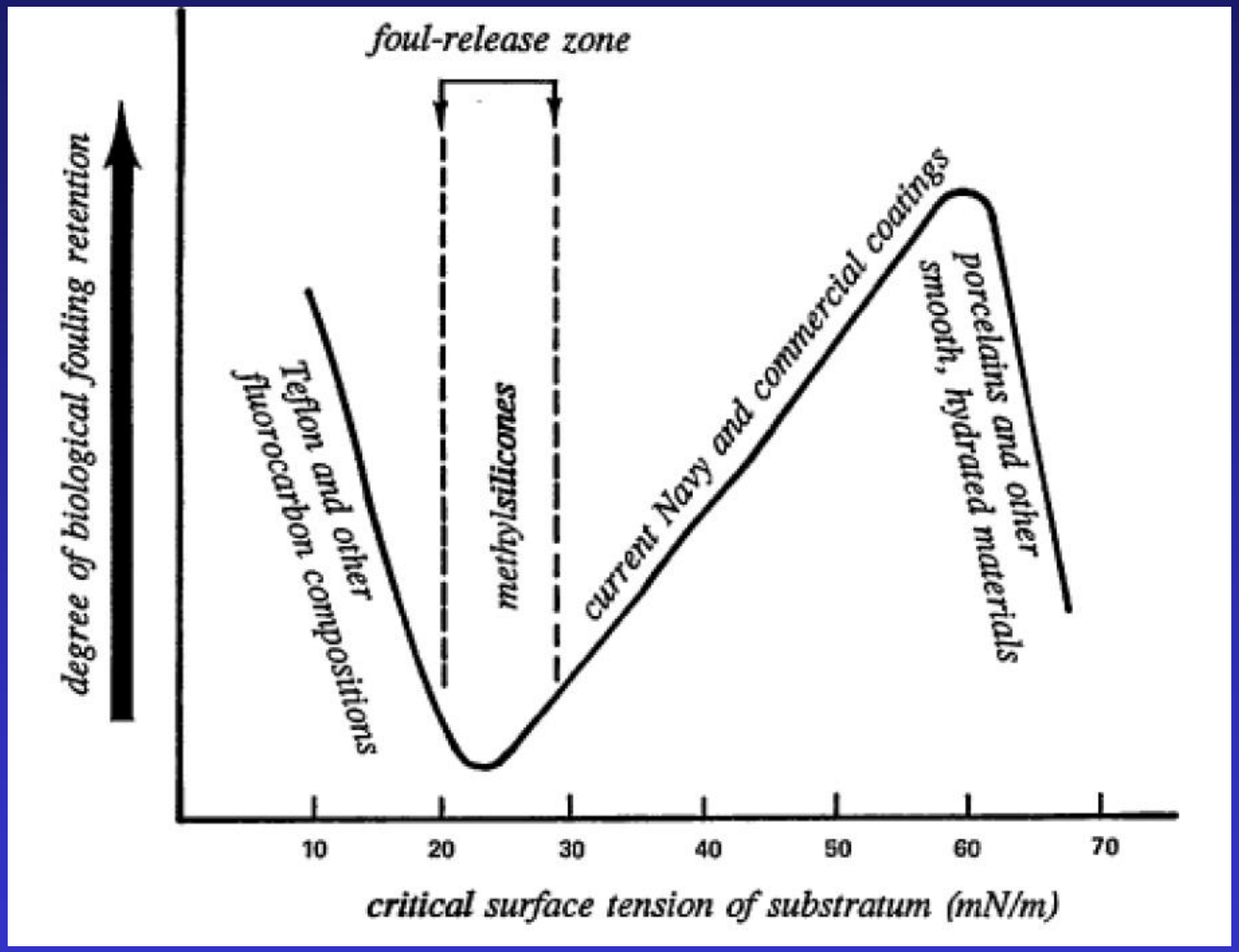
-Infection control strategies-

Surface modification approaches



Nino Papukasvilli, Hamburg 2012, PhD-Thesis

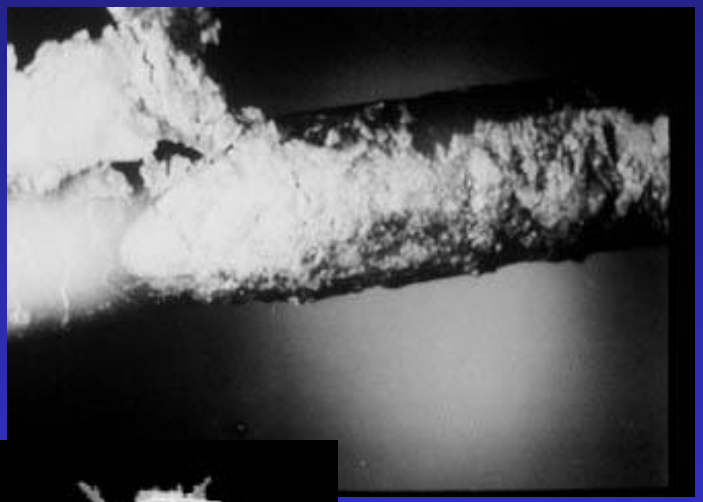
-Infection control strategies-
Surface modification – antiadhesion

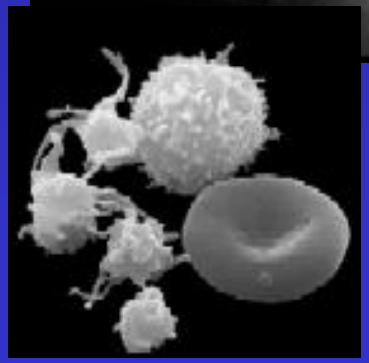


[75] R. E. Baier, „Surface behaviour of biomaterials: The *theta* surface for biocompatibility", *J. Mater. Scie: Mater. Med.*, **2006**, 17, 1057–1062.

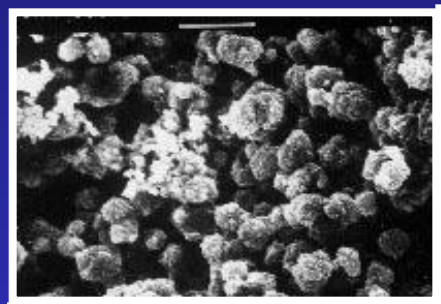
Catheter-associated infectious complications

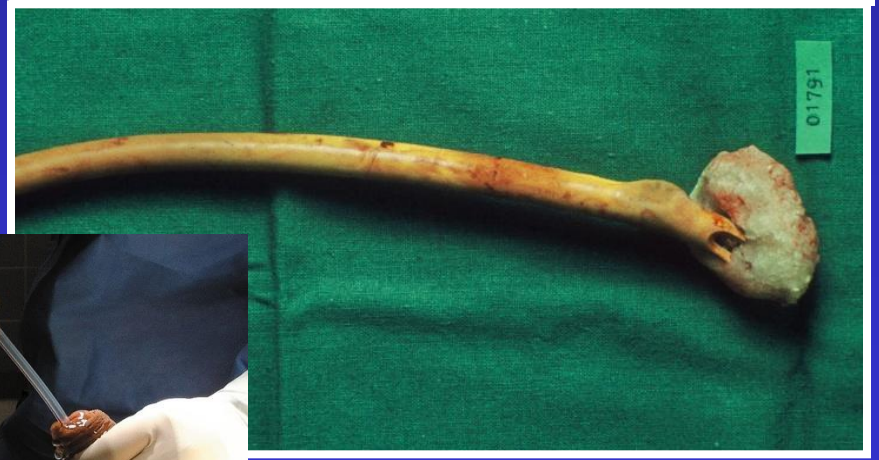
Thrombosis, calcification and Infection

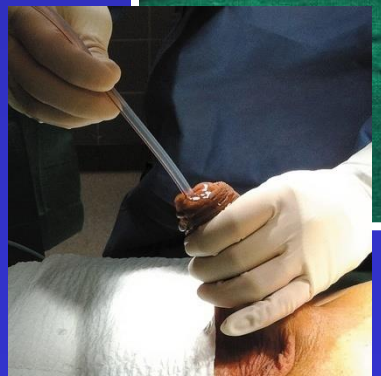




Incrustation and Infection



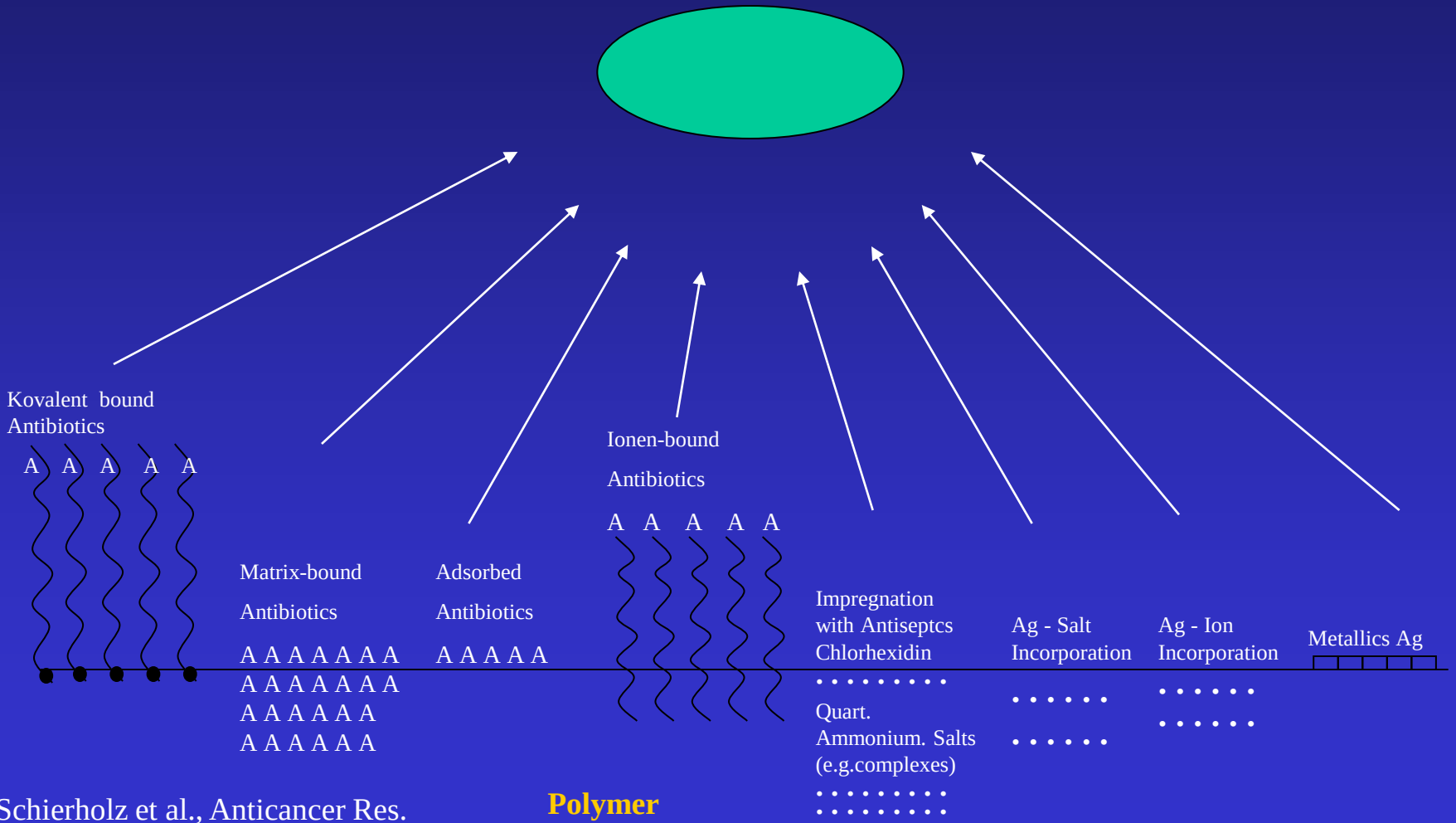




Infection control strategies-

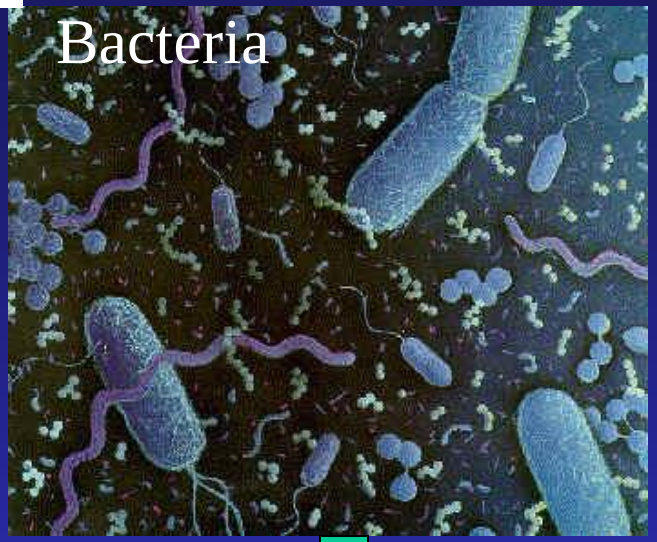
Antiinfective Materials

Target: colonizing microorganismen

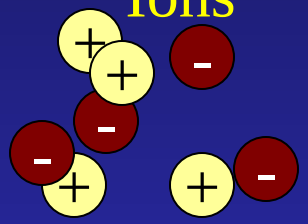


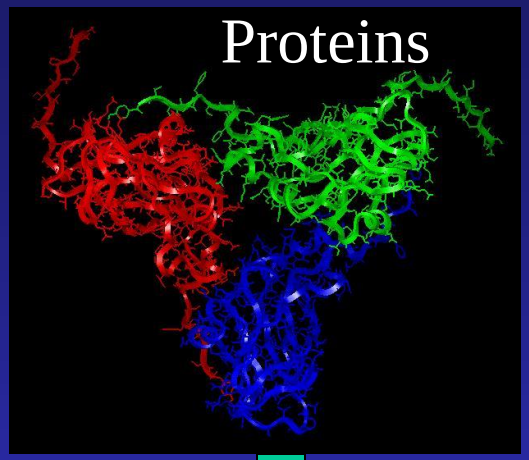
Schierholz et al., Anticancer Res. 1998

Encrustation – infection inhibiting surfaces



Fluid





F Cl OH COOH

Pentose-saccharide

Hepa-rine

Phosphoryl-choline

New Polymers e.g. Polysulfones

Surface Chemistry Hydrophobic-Hydriphilic

Nano- Microstructure (Lotus-effect)

Hydrogels

Coating

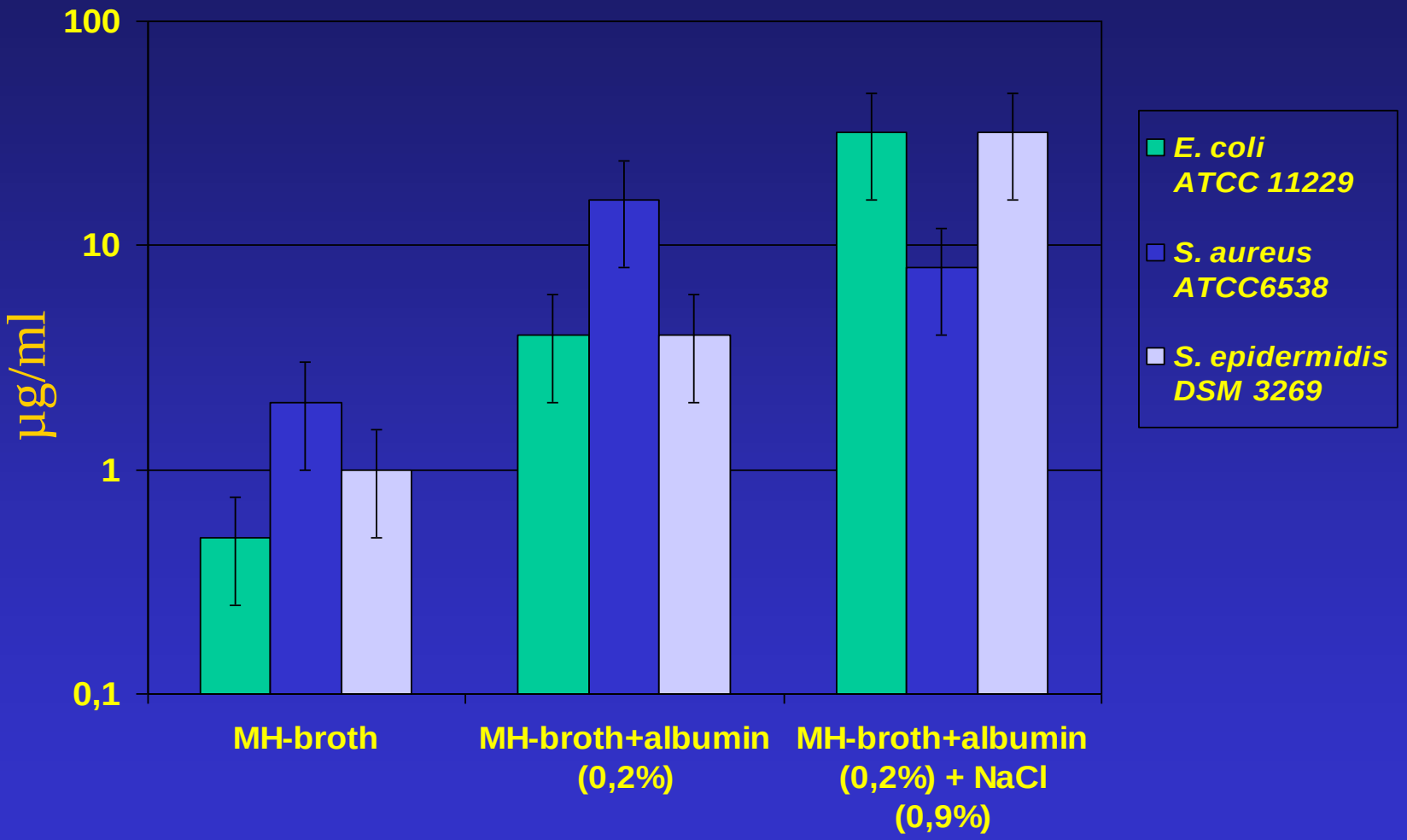
Ag

Anti septics

Anti biotics

Schierholz et al. Intern J.Antim.Chth.2002

Minimal inhibitory concentrations (MIC's) of silver nitrate in MH-broth with albumine (0,2 %) and in MH-broth containing albumine (0,2%) and NaCl (0,9%) to staphylococci and *E. coli*



MICs were rising more than 1,000% by addition of albumine and NaCl to MH-broth

Schierholz et al. Am.J.Med. 1999


20KV X1030 10U 101 02490 HV

In vivo efficacy of silver coated medical devices

Table 1. In vivo efficacy of silver-coated medical prostheses.

Type of prosthesis	Efficacy in animals	Efficacy in humans
Bladder catheters		
Coated with silver alone	Unknown	Controversial
Coated with silver hydrogel	Unknown	Moderately effective
Central venous catheters		
Affixed with silver-chelated cuff	Unknown	Effective with short-term but not long-term cuffed catheters
Coated with silver alone	Unknown	Ineffective
Silver iontophoretic catheter	Effective	Unknown
Coated with silver sulfadiazine–chlorhexidine	Effective	Moderately effective for short-term but not long-term access
Coated with silver sulfadiazine	Not effective	Unknown
Coated with silver–benzalkonium chloride	Unknown	Unknown
Peritoneal catheters		
Coated with silver alone	Effective	Unknown
Equipped with a silver ring	Unknown	Not effective
Vascular grafts coated with silver-antibiotic	Effective	Unknown
Silver-coated prosthetic heart valve sewing rings	Not effective	Unknown
Silver-coated external fixation pins	Not effective	Unknown
Silver-coated sutures	Unknown	Unknown

CID 1999;29 (December)

Tabelle 6: Kommerziell erhältliche ZVK-Typen (nach Hockenhull et al.[70])

Kategorie	Beschichtung	Extralumiale Beschichtung	Intralumiale Beschichtung
Antimikrobiell behandelte ZVK (erste Generation)	CHSS	Ja	Nein
	Silber	Ja	Nein
	SPK[1]	Ja	Nein
Antimikrobiell behandelte ZVK (zweite Generation)	Silber imprägniert	Ja	Ja
	Benzalkonium Chlorid imprägniert	Ja	Ja
	Silberimprägnierte Manschette	Ja	Ja
	CHSS Plus	Ja	
Antimikrobiell (antibiotisch bzw. antimykotisch/ antibiotisch) beschichtete ZVK	Minocyclin und Rifampicin	Ja	Ja
	Miconazol und Rifampicin	Ja	Ja

CHSS = Chlorhexidin, Silber-Sulfadiazin. SPK = Silber, Platin und Karbon (mit Freisetzung von Silberionen intra- und extraluminal). ZVK = Zentraler Venenkatheter.

1) SPK: Imprägnierung mit Silber, Platin und Karbon (mit Freisetzung von Silberionen intra- und extraluminal).

Hockenhull JC, Dwan K, Boland A, Smith G, Bagust A, Duendar Y, Gamble C, McLeod C, Walley T, Dickson R. The clinical effectiveness and cost-effectiveness of central venous catheters treated with anti-infective agents in preventing bloodstream infections: a systematic review and economic evaluation. Health technology assessment (Winchester, England) 2008; 12(12): 1-154.

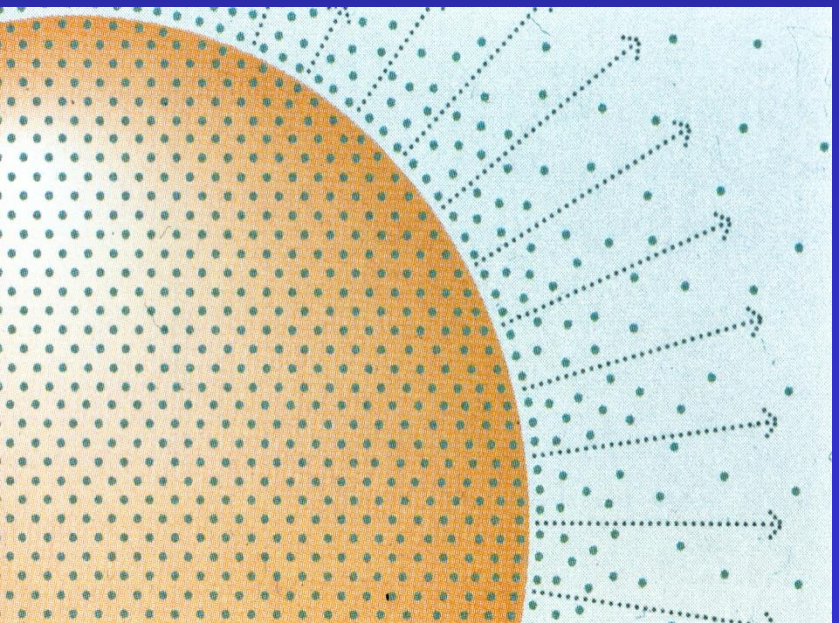
Local antimicrobial drug delivery

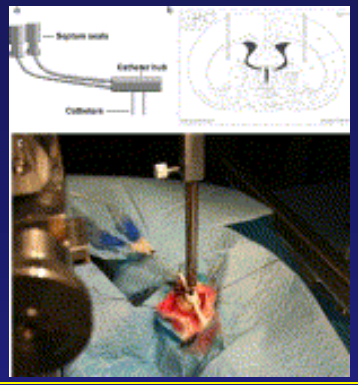
Coatings have mostly limited effects:

- Effective drugs ?

- in time (days – weeks?)

-in distance (µm- cm?)





Animal trial of rifampin releasing CSF shunts

Background

CSF-shunts are a principal source of recurrent infections (5-12%)

Objective

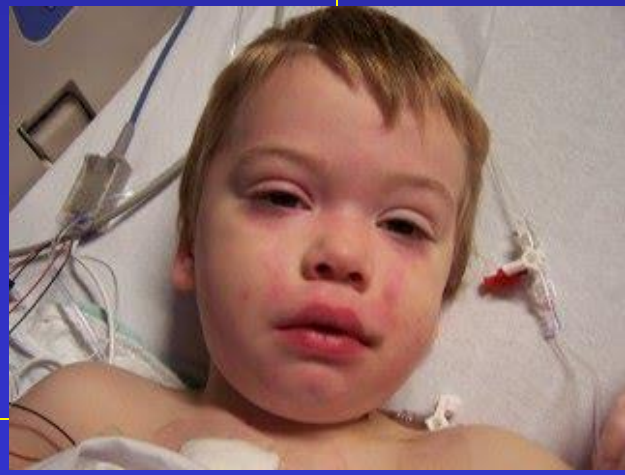
To determine the efficacy of catheters coated with rifampin (9%) in preventing catheter-related colonization and infections as well as adverse reactions

Design

Intrathecal implantation into rabbit ventricle system

Inoculation with appr. 10(5) CFU S.aureus

Sacrify after 2-6 weeks- microbiological and histological evaluation



Schierholz et al. 1992 ICAC, ***Schierholz et al. Biomaterials 1994, Hampl et al. Acta Neurochir. 1995***

Animal trial of intrathekal rifampin releasing shunts

Detection of S. aureus

	Catheter Segment	Brain Tissue	CSF	Blood
Untreated catheter	18/18	19/19	6/14	4/18
Rifampicin catheter	0/18	0/18	0/18	0/18

Hampl, Schierholz et al., ICAAC 1992/Acta Neurochir. 1995

The ideal local antimicrobial drug delivery

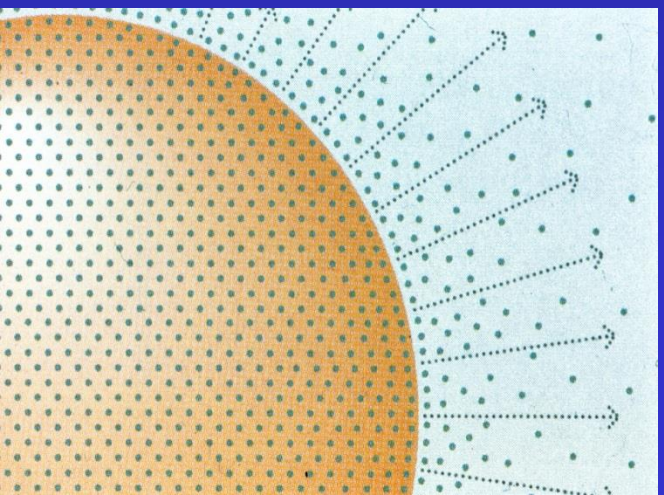
Covering a broad bacterial spectrum

Bactericidal activity

Killing of dormant bacteria

No ICU "firstline" antibiotics

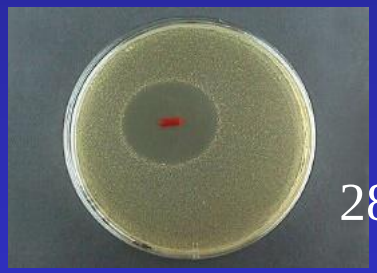
Synergistic combinations



- CHX-silver-sulfadiazine 1st 2nd generation
- Rifampin-Minocycline
- Rifampin-Miconazole

Supersaturated matrix drug delivery approach

1d



28d

As much* as possible (>15mm *(Sheretz 1993))

As long* as possible(>1 week *(Schierholz 1994))

As biocompatible* as possible *(Schierholz 2001)

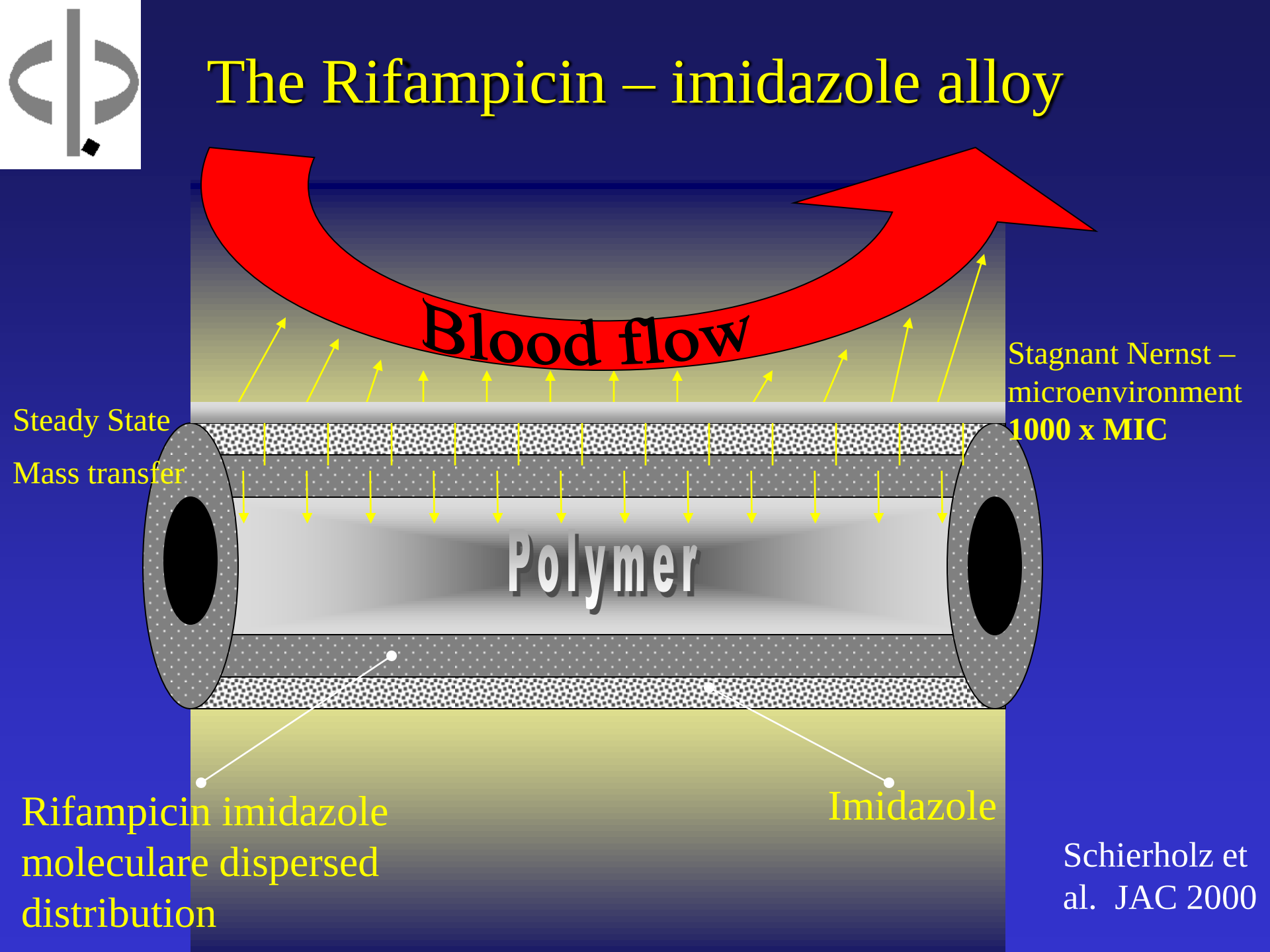
-constant elution for more than 2 weeks after the burst effect

-serumlevel not detectable(< <1ug/ml)

-no renal excretion, no excretion via urin

Rump et al JAC 2001

The Rifampicin – imidazole alloy



Schierholz et al. JAC 2000

Antimicrobial Activity of rifampin-miconazole loaded catheters(in vitro)

		Rifampicin/Miconazol loaded	Sivber Sulfadiazin/Chlorhexidin coated
Gram positiv	S.epidermidis	33,0 (±6.0)	16,1 (±1,5)
	S. aureus	26,0 (±3,1)	13,0 (±1,2)
	E. faecalis	17,0 (±3,5)	7,0 (±3,0)
Gram negativ	P. aeruginosa	10,9 (±4,0)	3,0 (±2,0)
	E.coli	14,5 (±3,2)	11,0 (±3,1)
	Enterobacter sp.	11,0 (±3,0)	5,3 (±1,2)
	C. albicans	14,0 (±3,1)	6,9 (±2,1)

Inhibition diameter mm

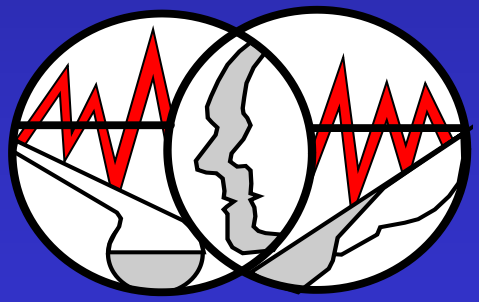
Schierholz et al. JAC (2000) 46: 45-50

Miconazol und Rifampin coated catheters –Results of a clinical trial

N. Yücel, M. Max, R. Roissant, R. Schwarz, J. Beuth, A. Bach, J. Schierholz, G. Pulverer, E. Neugebauer

Catheter Study Group 2000-2002

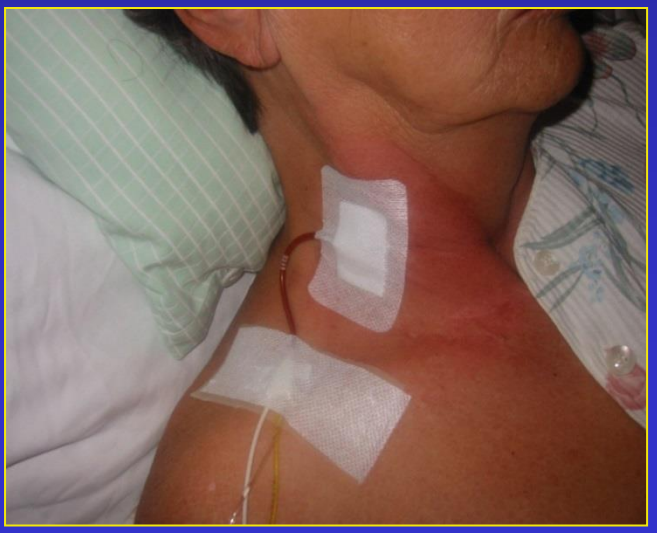
Aachen - Bonn - Heidelberg - Köln

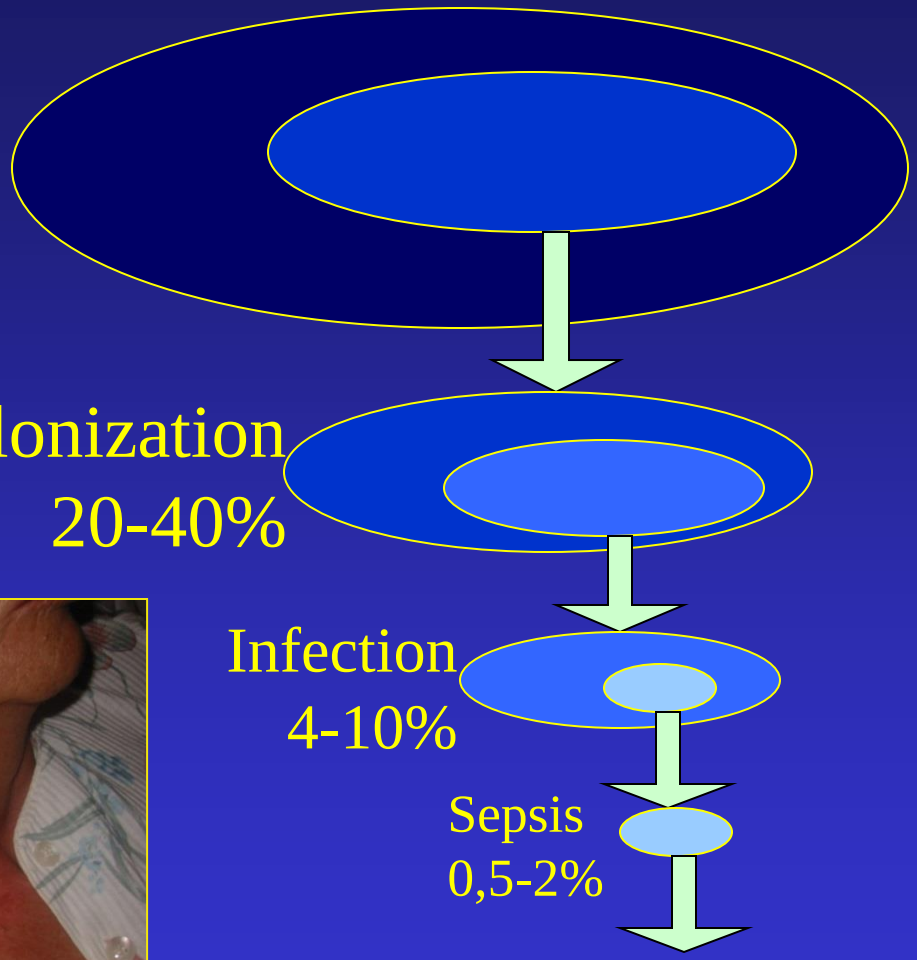


Study design

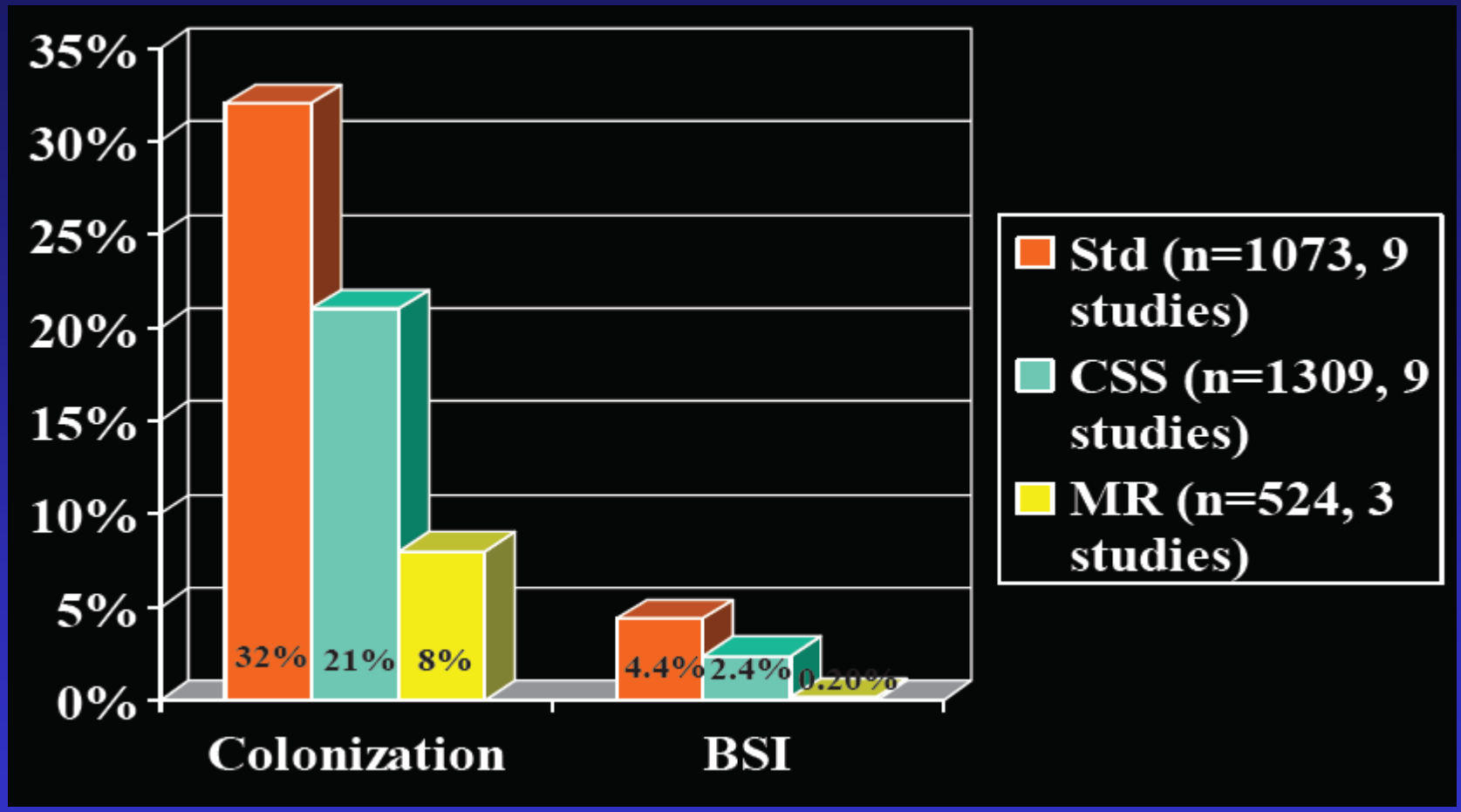
- Multicenter (2 university hospitals)
- Prospective, randomized, unblinded
- Enclosed 300 patients,
  early termination
- Interim analysis with 78 catheters
  Colonization, infection, CRBSI

Study objectives-Indwelling CVCs





Association Colonization-CRBSI-a Meta Analysis



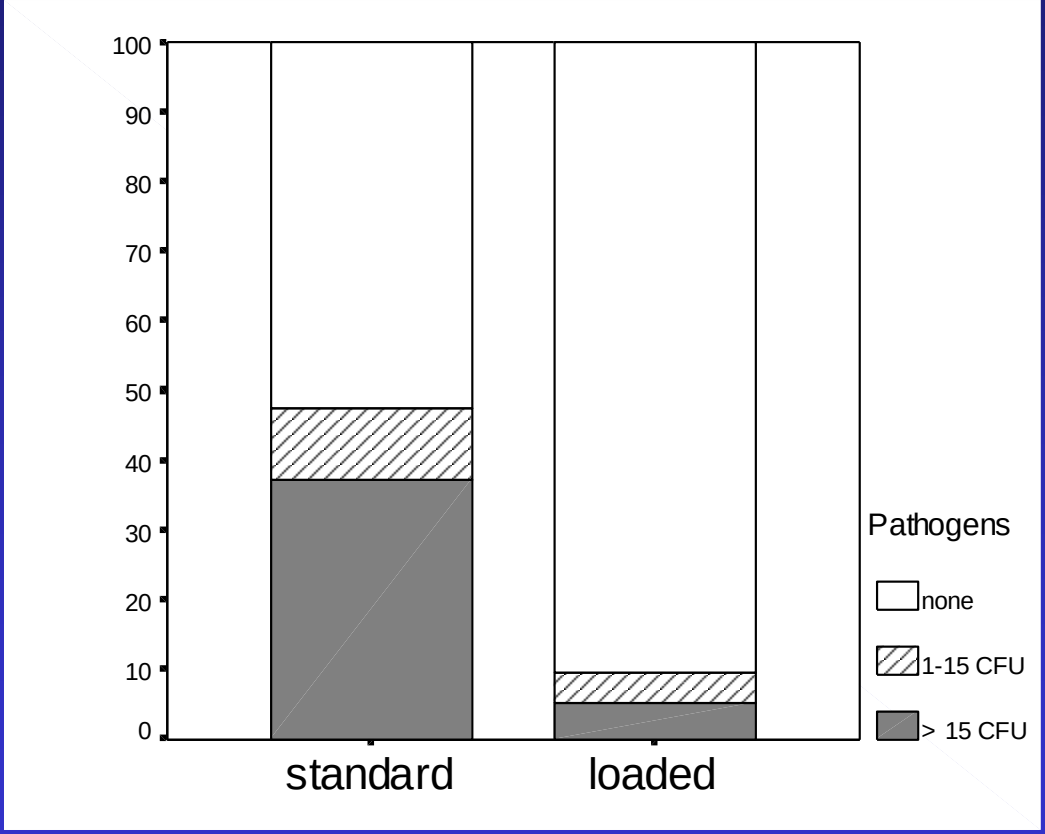
Eggimann T, Pittet D. Advances Sepsis 2000;1:2-15

Pathogens on standard- and loaded catheters

Microorganism	*standard*	*loaded*
- Staphylococcus epidermidis	*22*	*1*
- Staphylococcus aureus	*3*	*-*
- coagulase-negative Staphylococci	*4*	*-*
- other Staphylococci	*4*	*-*
- Enterococcus faecalis / cloacae	*2*	*3*
- Escherichia coli -	*1*	
- Klebsiella oxytoca	*-*	*1*
- Serratia marcescens	*2*	*-*
- Acinetobacter baumannii / lwoffii	*3*	*-*
- Pseudomona aeruginosa	*1*	*-*
- Corynnebacterium	*-*	*1*
- Candida sp.	*2*	*-*

Yuecel et al. JAC 2004

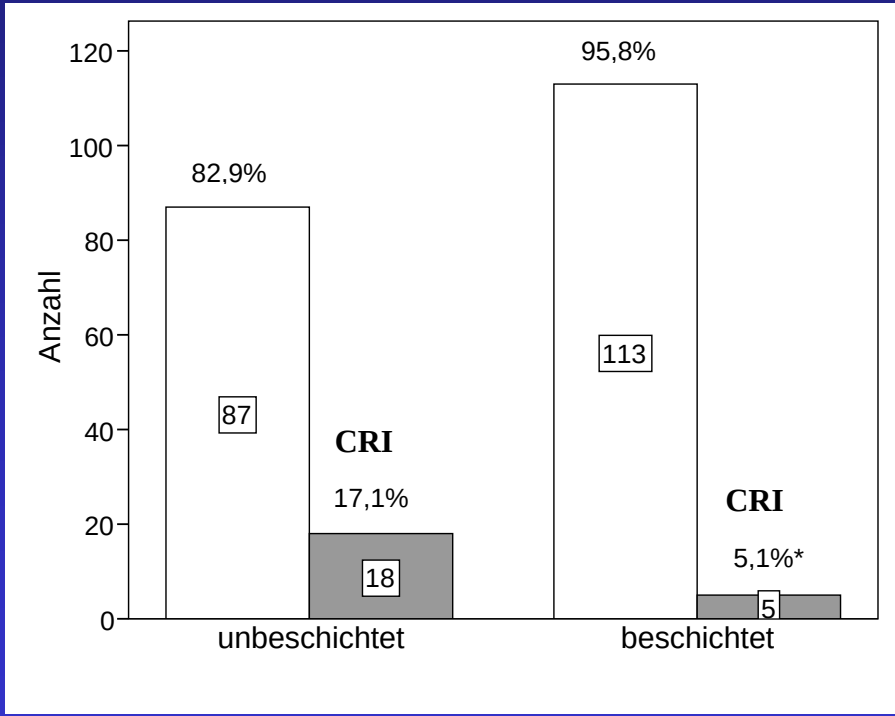
Presence of pathogens at the R/MC CVC

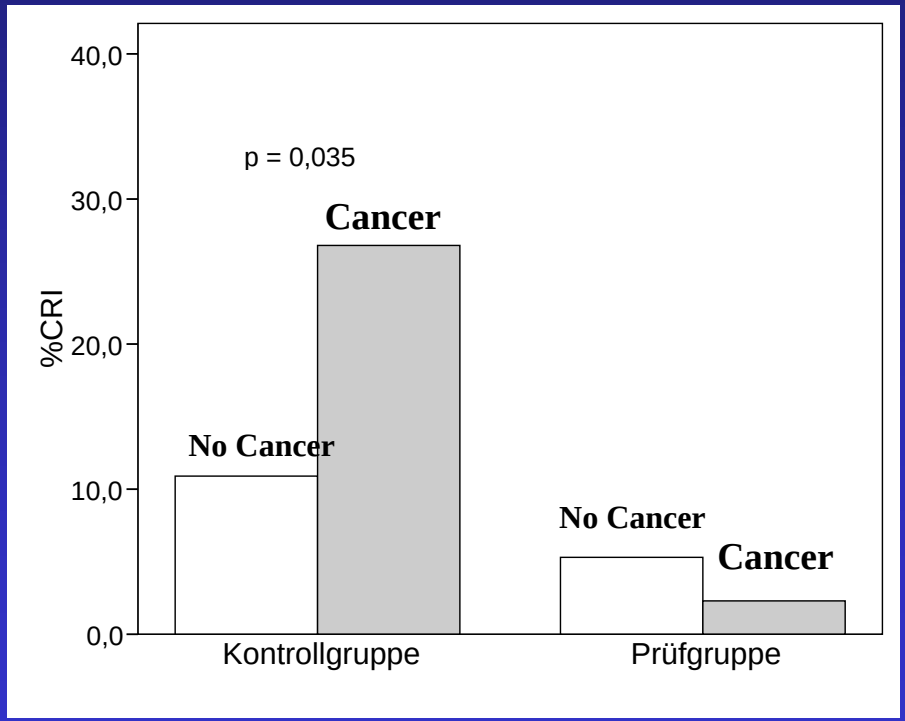


Yuecel et al., JAC 2004

Colonization rate (>15CFU):-86%, p<0,0001

R/MC Catheter related infection rate



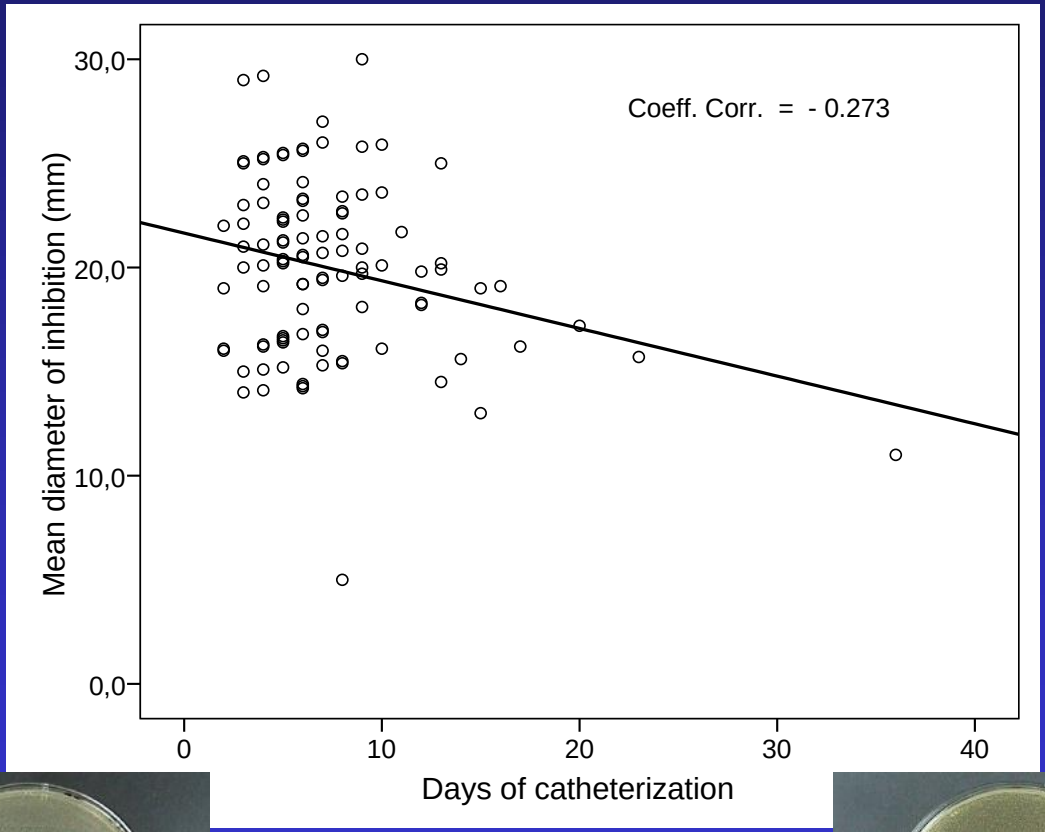


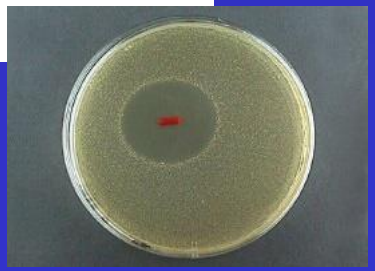
Clinical Infection rate:- 76% p<0,002

Oncology:-91.4%, p<0,001

Nagelschmidt et al. Anticancer Res. 2010/ Yuecel et al. JAC 2004

Antibiotic activity of the modified catheters after removal (n = 102)





Nagelschmidt et al. Anticancer Res. 2010

Reduction of CBSI using R/MC catheters

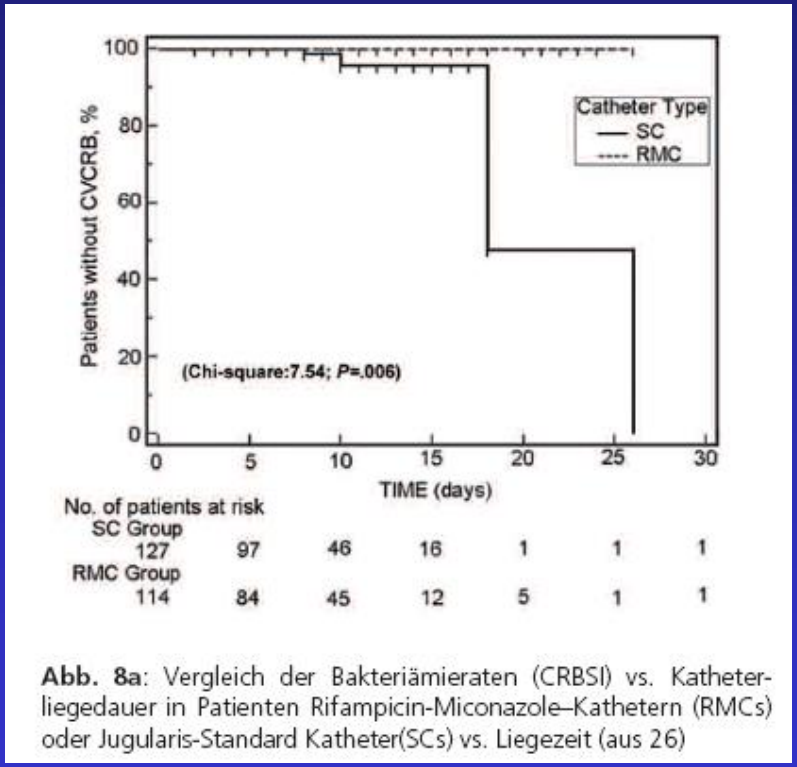


Abb. 8a: Vergleich der Bakteriämieraten (CRBSI) vs. Katheter-liegedauer in Patienten Rifampicin-Miconazole–Kathetern (RMCs) oder Jugularis-Standard Katheter(SCs) vs. Liegezeit (aus 26)

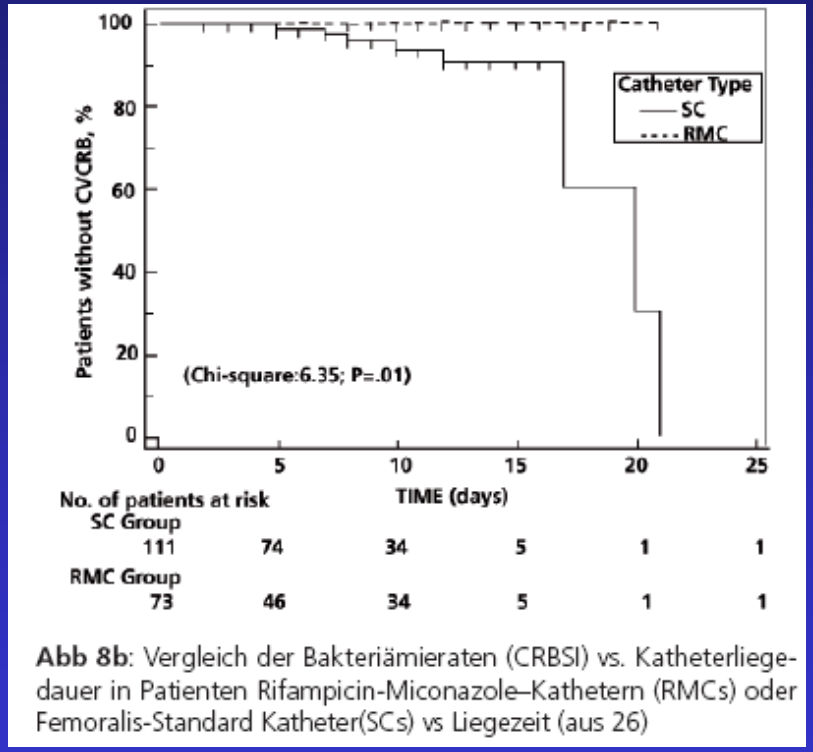


Abb 8b: Vergleich der Bakteriämieraten (CRBSI) vs. Katheterliege-dauer in Patienten Rifampicin-Miconazole–Kathetern (RMCs) oder Femoralis-Standard Katheter(SCs) vs Liegezeit (aus 26)

CRBSI rates: 0 vs. 8,6/1000 catheter days, p<0,006

Lorente et al. J. Clin.Inf. 2008

Controlled clinical studies on antimicrobial central venous catheters (according to Falagas et al.).

Relative risk reduction (RRR) of bacterial colonization

1rst Autor	Year	Ref.	Groups	N1/N2	RRR
Raad	1997		RMI/STD	130/136	69.2%
Chatzinikolaou	2003		RMI/STD	66/64	20.0%
Leon	2004		RMI/STD	187/180	56.8%
Hanna	2004		RMI/STD	-	-*
Darouiche	1999		RMI/CSS	356/382	65.2%
Fraenkel	2006		RMI/SPC	280/294	40.0%
Darouiche	2005		RMI/STD	166/146	10.7%
Yücel	2004		RMO/STD	118/105	84.6%

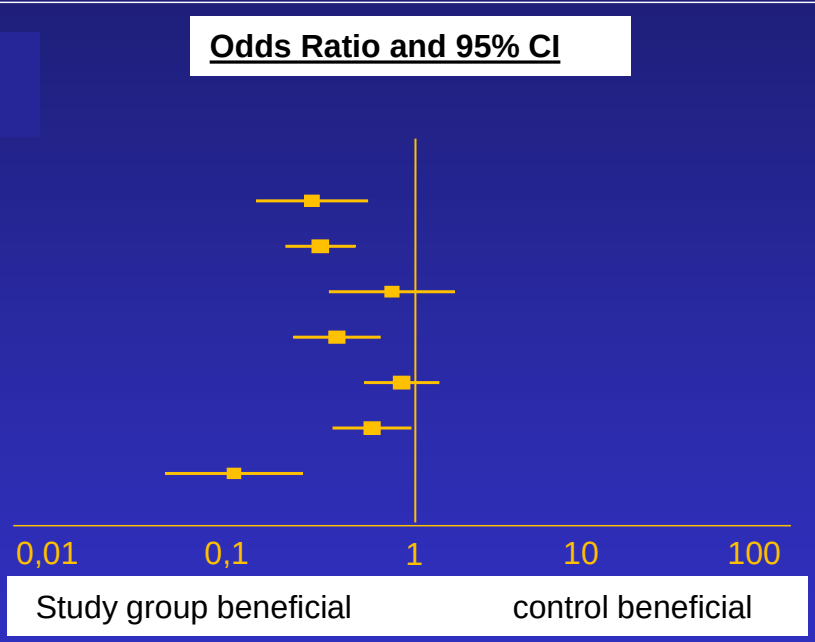
CVCs studied: STD: standard without drugs, RMI: rifampicin-minocycline, RMO: rifampicin-miconazole, CSS: chlorhexidine silversulfadiazine, SPC: silver/platinum/carbon. N: number of patients per group

•only bloodstream infection reported

Falagas ME, Fragoulis K, Bliziotis IA, Chatzinikolaou I: Rifampicin-impregnated central venous catheters: a meta-analysis of randomized controlled trials. J Antimicrob Chemother 2007; **59**: 359-369.

Meta –Analysis of clinical studies of rifampicin-minocycline (RMI) - and rifampicin-miconazole catheters: Forest plot of catheter colonization

Studie	Jahr	Odds Ratio	Unteres Limit	Oberes Limit
Raad	1997	0,260	0,124	0,546
Darouiche (a)	1999	0,290	0,181	0,464
Chatzinikolaou	2003	0,740	0,322	1,701
Leon	2004	0,360	0,201	0,644
Darouiche (b)	2005	0,840	0,509	1,387
Fraenkel	2006	0,570	0,337	0,963
Yücel	2004	0,094	0,038	0,234



According to Falagas et al. 2007, completed by study data of Yuecel and Nagelschmidt et al.2010

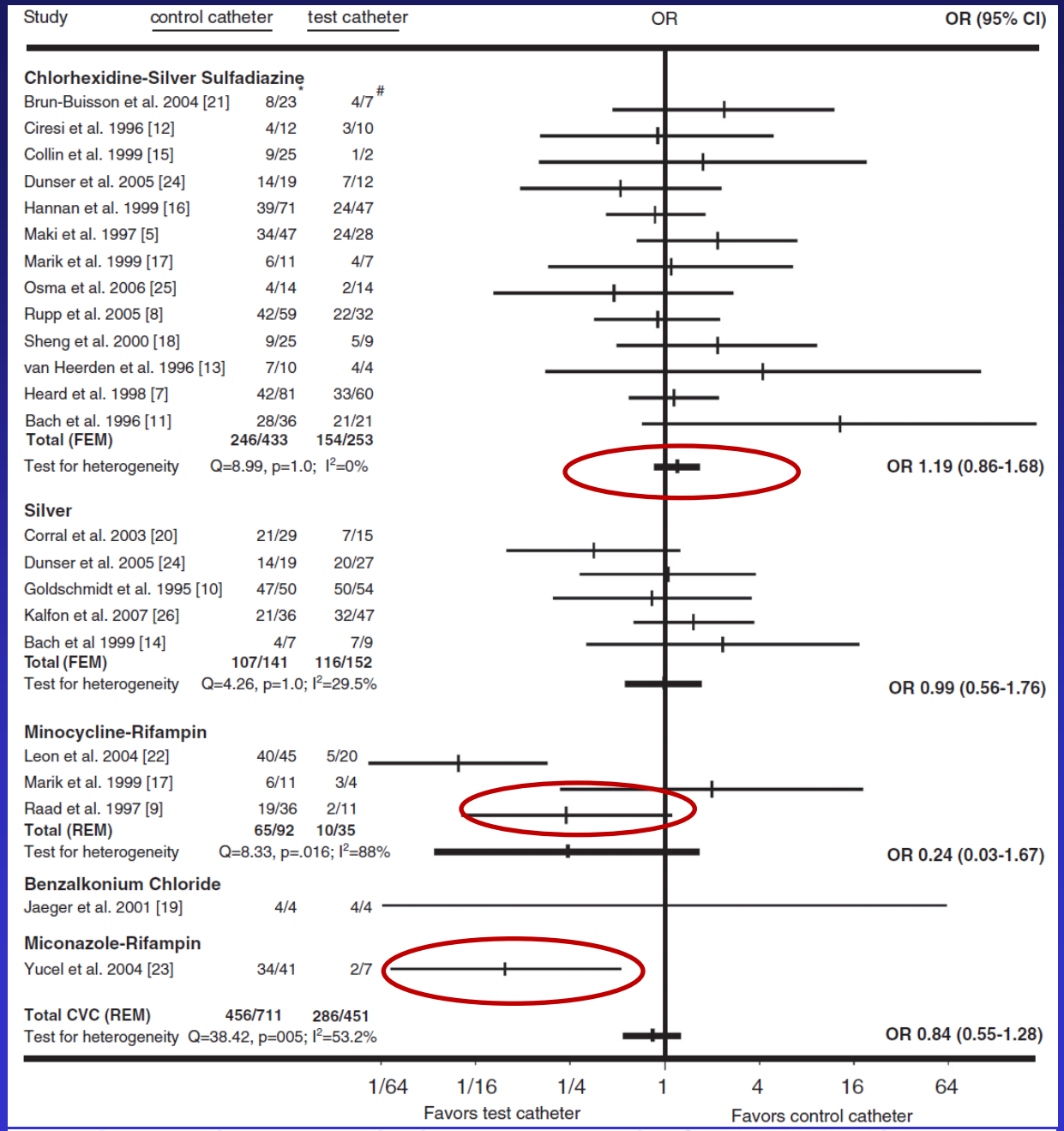
Colonization rates of antibacterial catheters

Table 2 Rates of colonization of the study and control catheters

Study	Mean catheter dwell time (test catheter days vs. control catheter days)	Number of CVC studied (test vs. control)	Colonization	
			n	Rate per 1000 days
Goldschmidt et al. 1995 [10]	13.3 vs 12.7	120 vs 113	54 (45.1%) vs 50 (44.2%)	33.8 vs 34.8
Bach et al. 1996 [11]	7.8 vs 7.8	116 vs 117	21 (18.1%) vs 36 (30.8%)	23.2 vs 39.4
Ciresi et al. 1996 [12]	12.9 vs 11.5	124 vs 127	10 (10.9%) vs 12 (12.1%)	6.3 vs 8.2
van Heerden et al. 1996 [13]	6.6 vs .6.8	28 vs 26	4 (14.3%) vs 10 (38.5%)	21.6 vs 56.6
Maki et al. 1997 [5]	6 vs 6	208 vs 195	28 (13.5%) vs 47 (24.1%)	22.4 vs 40.2
Heard et al. 1998 [7]	8.5 vs 9.0	151 vs 157	60 (39.7%) vs 81 (51.6%)	46.7 vs 57.3
Bach et al 1999 [14]	4.5 vs 2.3	34 vs 33	9 (26.5%) vs 7 (21.2%)	58.8 vs 52.2
Collin et al. 1999 [15]	9.0 vs 7.3	98 vs 139	2 (2.0%) vs 25 (18%)	2.3 vs 24.6
Hannan et al. 1999 [16]	7.5 vs 7.6	174 vs 177	47 (27.2%) vs 71 (40.2%)	36.0 vs 52.8
Marik et al. 1999 [17]	6 vs 6 vs 6	36 vs 38 vs 39	7 (19.4%) vs 4 (10.5%) vs 11 (28.2%)	32.4 vs 17.5 vs 47.0
Sheng et al. 2000 [18]	9.1 vs 8.2	113 vs 122	9 (7.1%) vs 25 (20.5%)	8.8 vs 25
Jaeger et al. 2001 [19]	14.8 vs 19.3	25 vs 25	4 (16.0%) vs 4 (16.0%)	10.8 vs 8.3
Corral et al. 2003 [20]	12 vs14	103 vs 103	29 (28.2%) vs 41 (39.8%)	23.5 vs 27.7
Brun-Buisson et al. 2004 [21]	10.5 vs 12.0	188 vs 175	7 (3.7%) vs 23 (13.1%)	3.6 vs 11.0
Leon et al. 2004 [22]	10.3 vs 10.4	187 vs 180	20 (10.7%) vs 45 (25.0%)	10.4 vs 24.0
Yucel et al. 2004 [23]	7.5 vs 6.7	118 vs 105	6 (5.1%) vs 38 (36.2%)	6.8 vs 54.0
Dunser et al. 2005 [24]	9.3 vs 9.7 vs 10.7	160 vs 165 vs 160	27 (16.9%) vs 12 (7.3%) vs 19 (11.9%)	18.1 vs 7.5 vs 11.9
Rupp et al. 2005 [8]	6.9 vs. 6.7	384 vs 393	32 (9.3%) vs 59 (16.3%)	12.1 vs 22.4
Osma et al. 2006 [25]	11.7 vs 8.9	64 vs 69	14 (21.9%) vs 14 (20.3%)	18.7 vs 22.8
Kalfon et al. 2007 [26]	13.1 vs 12.9	320 vs 297	47 (14.7%) vs 36 (12.1%)	11.2 vs 9.4
Raad et al. 1997 [9]	6 vs 6	130 vs 136	11 (8·5%) vs 36 (26·5%)	14.1 vs 44.1

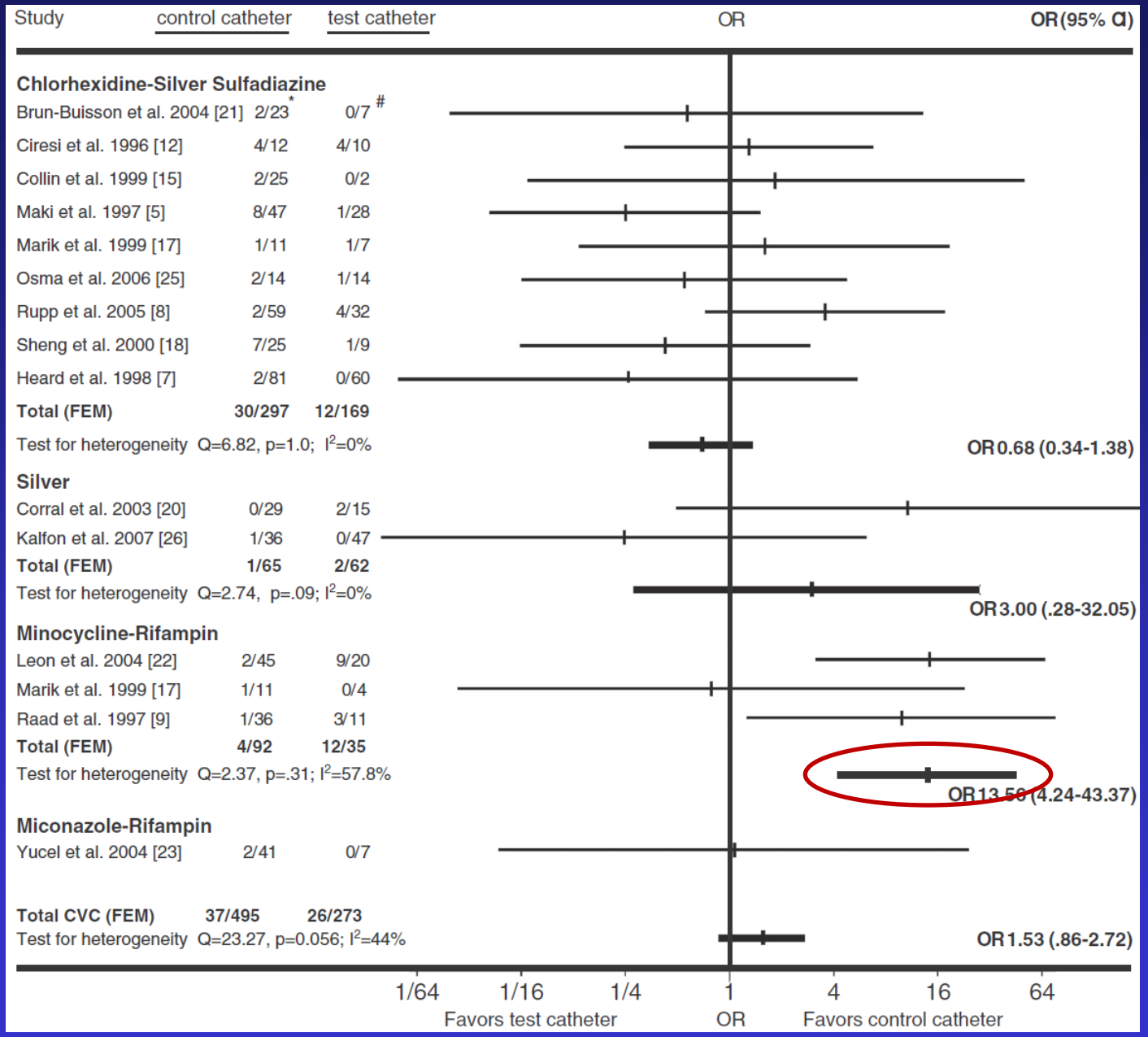
Novikov *et al. Antimicrobial Resistance and Infection Control* 2012, **1**:40

Colonization rates of antibacterial catheters



Novikov *et al. Antimicrobial Resistance and Infection Control* 2012, **1**:40

Candida Colonization rates of antibacterial catheters



Novikov *et al. Antimicrobial Resistance and Infection Control* 2012, **1**:40

Medizinische Wirksamkeit und Kosten-effektivität von Minocyclin/Rifampicin-beschichteten zentralvenösen Kathetern zur Prävention von Blutbahn-infektionen bei Patienten in intensiv-medizinischer Betreuung

Silke Neusser, Eva Maria Bitzer, Ingeborg Mieth, Christian Krauth

DIMDI
deutsche agentur für HTA des
Deutschen Instituts für Medizinische
Dokumentation und Information

Trotz deutlicher methodischer Unterschiede weisen alle RCT auf protektive Effekte der MR-beschichteten ZVK im Vergleich zu herkömmlichen ZVK, aber auch im Vergleich zu anderen antimikrobiell beschichteten ZVK, hin. Diese sind allerdings oftmals statistisch nicht signifikant. Die Metaanalysen der systematischen Übersichtsarbeiten bestätigen die protektiven Effekte.

Gesundheitsökonomische Bewertung

Insgesamt liegen eine Kohortenstudie und drei Entscheidungsmodelle vor. Dabei handelt es sich um gesundheitsökonomische Studien, die auf der Basis von Primärstudien und konservativen Modellrechnungen zu Kosteneinsparungen durch den Einsatz MR-beschichteter ZVK kommen. Aussagen zur attributablen Mortalität sind aufgrund der heterogenen Modellgüte und widersprüchlicher Ergebnisse nicht möglich.

Recommendations for antimicrobial CVCs

CDC: Use of antibacterial catheters in adults when:

- >5 days indwelling time
- CRBSI rate > 3.3/1000 catheter days

epic2: National evidence-based guidelines: high risk for CRBSI and 1-3 weeks indwelling time

AWMF Leitlinie: High risk patients, neonatal ICU, Immuno-compromized pts., TPN, Hemato-oncology, Dialysis, Burns, >5 days indwelling time

AWMF guidelines, GMS German Medical Science;7:Doc19. DOI: 10.3205/000078, URN: urn:nbn:de:0183-0000787, 2009

CDC: Prevention of catheter infection MMWR 2002,51/2010

Anti-infective osteosynthesis plates in traumatology

(cooperation Bochum Bergmannsheil)

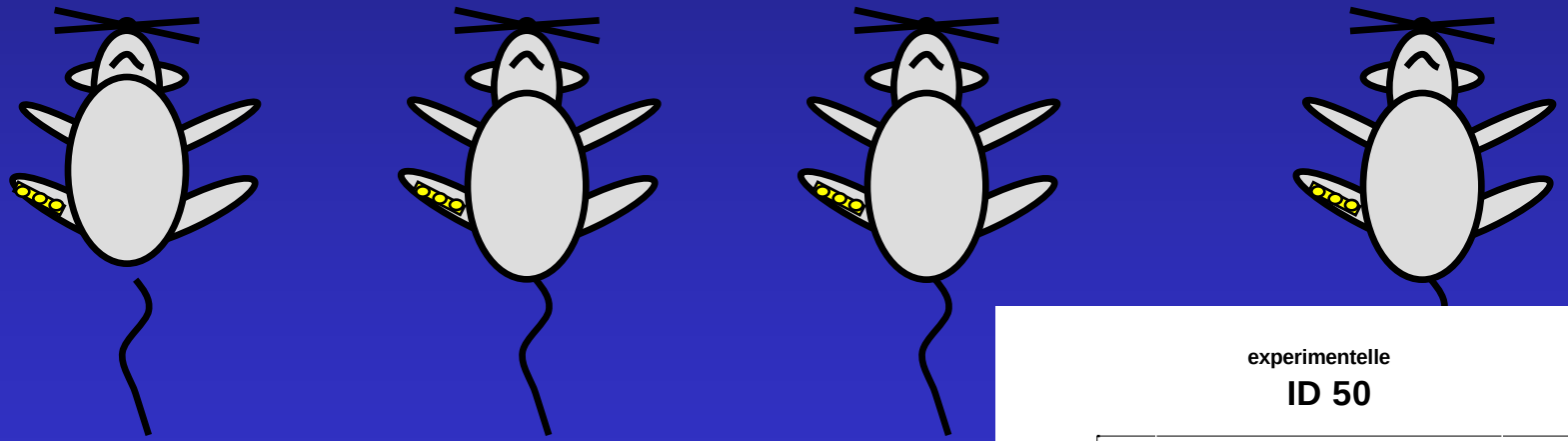
Implantation of Ti-plates into left rat tibia

Ti pure

Ti + PLLA

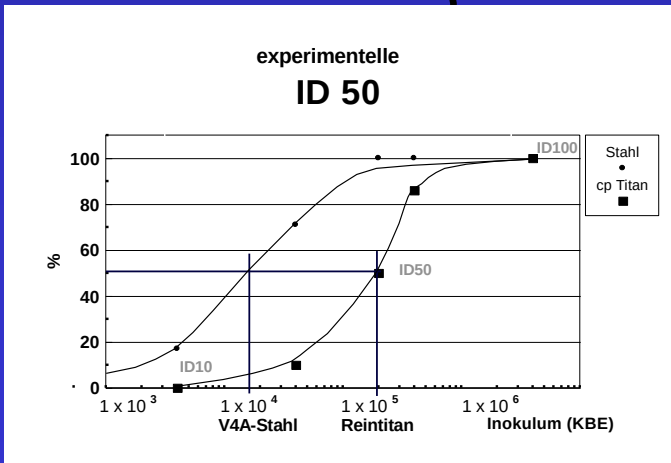
Ti + PLLA +Rif/Fus

Ti + PLLA +Oct/Irg

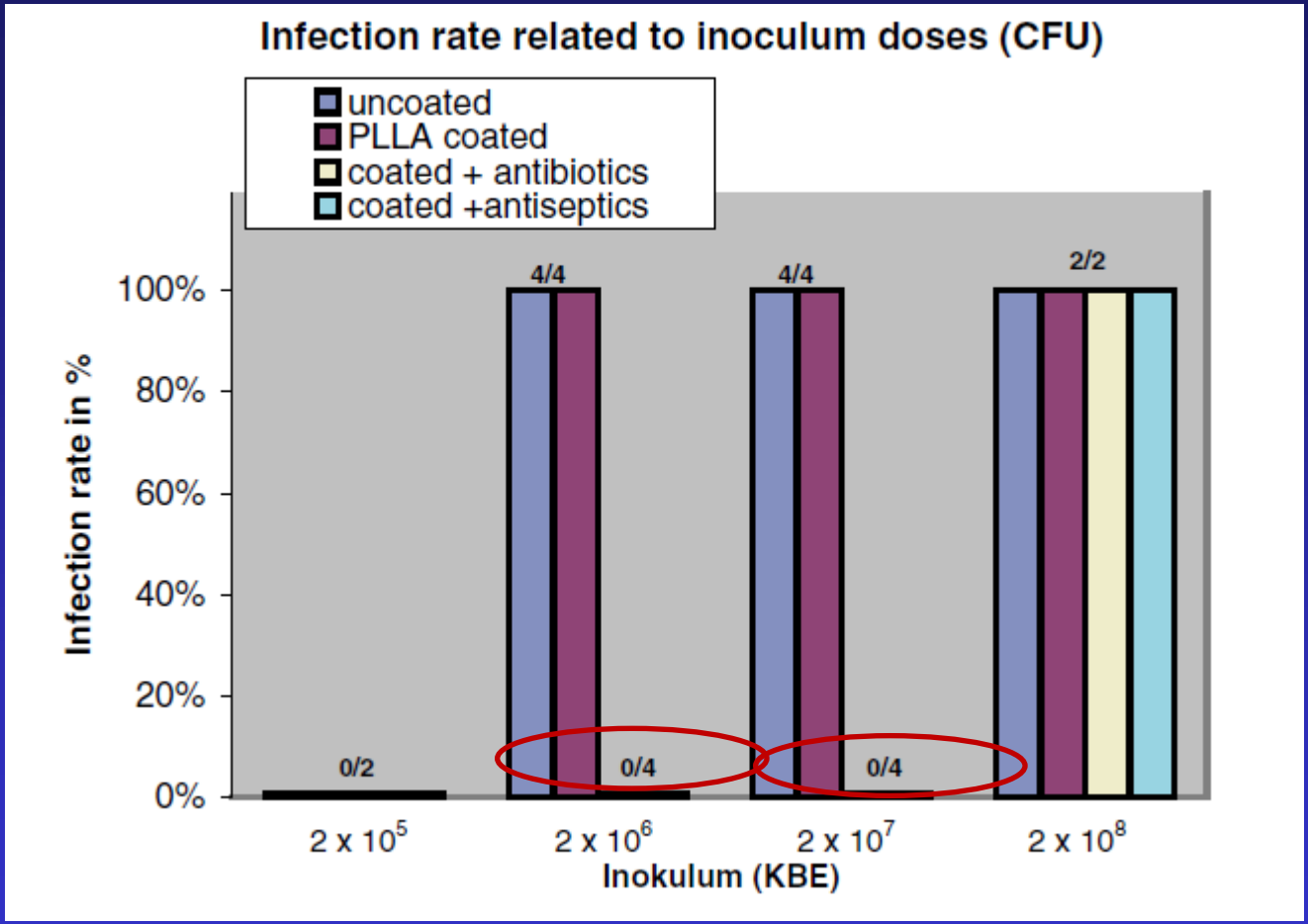


Inoculation by LD_{50} (10^5 CFU S.aureus)

→ 28d : sacrify-Microbiology of implant and implant-related tissue, microbiological evaluation of femur, spleen, liver and brain



Results



ID50 values groups I and II without antibacterial coating **IxI10^6 CFU** (p=0.033)

Kaelicke et al. J. Orthop. Res. 2006, vol. 24, n8, pp. 1622-1640

Creating the ideal slow delivery system-steps to registration

- —The full complement of biocompatibility tests should be considered for all devices that contact body fluids and tissues.(In accordance to ISO 10993/EN 30993 standard, FDA Blue Book Memorandum G95-1.)
- —The device modification and drug must remain stable under normal storage and use conditions and must have a reasonable shelf life.
- —Any device modification should provide drug in sufficient quantities over the needed time period.
- —The device treatment must be able to withstand the rigors of the insertion process and any subsequent device manipulation after placement.
- —Commercial products must be packaged and sterilized without diminishing the efficacy of the antibiotic, antimicrobial, antithrombogenic or antiproliferative agent.

Drug-Device Regulation

Under

EC DG XXIV –Guidelines MEDDEV 2 1/3 revision 5 (1998)

EU Medical Devices Directive

- Major principle: A product is regulated under one system or another:
- Application as an device if the pharmaceutical is anciliary
- **- the assessment of the pharmaceutical is performed by the medicine regulatory authority**

Most Coatings Fail on the way to the market - Why ?

- Design of coating ✔
- In vitro/safety ✔
- In vitro/efficacy ✔
- Human clinical trials ✔
- Regulatory ✔
- Manufacturing ✔
- Patent ✔
- costs ✔


Thank you
Primum nihil nocere